The Value of Family History as a Risk Indicator for Venous Thrombosis

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Background: A positive family history of venous thrombosis may reflect the presence of genetic risk factors. Once a risk factor has been identified, it is not known whether family history is of additional value in predicting an individual's risk. We studied the contribution of family history to the risk of venous thrombosis in relation to known risk factors.

Methods: In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis, a population-based case-control study, we collected blood samples and information about family history and environmental triggers from 1605 patients with a first venous thrombosis and 2159 control subjects.

Results: A total of 505 patients (31.5%) and 373 controls (17.3%) reported having 1 or more first-degree relatives with a history of venous thrombosis. A positive family history increased the risk of venous thrombosis more than 2-fold (odds ratio [95% confidence interval], 2.2 [1.9-2.6]) and up to 4-fold (3.9 [2.7-5.7]) when more than 1 relative was affected. Family history corresponded poorly with known genetic risk factors. Both in those with and without genetic or environmental risk factors, family history remained associated with venous thrombosis. The risk increased with the number of factors identified; for those with a genetic and environmental risk factor and a positive family history, the risk was about 64-fold higher than for those with no known risk factor and a negative family history.

Conclusions: Family history is a risk indicator for a first venous thrombosis, regardless of the other risk factors identified. In clinical practice, family history may be more useful for risk assessment than thrombophilia testing.

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A POSITIVE FAMILY HISTORY OF venous thrombosis may reflect the presence of genetic risk factors in a family. Carriers of a genetic risk factor are at increased risk of a first venous thrombosis, particularly when exposed to environmental triggers. For example, factor V Leiden synergistically increases the risk of venous thrombosis among oral contraceptive users.[1] Because universal screening is not cost-effective,[2,3] research efforts are focused on selection criteria that may be used to increase the chance of finding a genetic risk factor. Family history is an evident candidate.

Several authors have studied the value of family history as a surrogate of known genetic risk factors for venous thrombosis.[4-8] These studies have shown that the family history cannot be used to identify genetic risk factors because positive predictive value and sensitivity are low.

Few have studied the association between family history and venous thrombosis.[9,10] In addition, it is not known whether family history is of additional value in predicting an individual's risk of venous thrombosis once a genetic risk factor is identified. We therefore estimated the relative risk of venous thrombosis when the family history is positive and studied the contribution of family history to risk in strata of known risk factors. Family history was evaluated among patients with venous thrombosis and control subjects from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis, a large population-based case-control study.

METHODS

STUDY POPULATION AND DATA COLLECTION

Recruitment, data collection, and ascertainment of venous thrombosis events in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis have been

described in detail previously.[11,12] Study patients experienced a first deep venous thrombosis of the leg or pulmonary embolism between March 1, 1999, and August 31, 2004. Control subjects were partners of patients or random population control subjects. The random control subjects were recruited by random digit dialing[13] between January 1, 2002, and December 1, 2004, and frequency matched on sex and age to the patient group. All participants completed a questionnaire on risk factors for venous thrombosis and family history. Three months after discontinuation of vitamin K antagonist therapy, a blood sample was taken from patients who were diagnosed until June 1, 2002, and their partners. Patients with an indication for lifelong treatment with vitamin K antagonists were invited for a blood draw 1 year after the index date. Patients who were diagnosed from June 1, 2002, onward and their partners received a cotton swab along with their questionnaire for collecting buccal cells; data from these participants were not included in the present study. In the random population control group, blood samples were collected after the questionnaire was returned. Overall response rates were 83.4% in the patient group, 81.6% in the partner control group, and 69.0% in the random population control group.

FAMILY HISTORY

Participants were asked whether their parents, brothers, or sisters had experienced venous thrombosis and, if so, their age at the event. Because partners of patients were recruited as control subjects, offspring was not included in the family history definition. Family history was considered positive if at least 1 of these first-degree relatives had experienced venous thrombosis. Within this group, participants with a strong indication of genetic predisposition were defined as having at least 1 first-degree relative affected before age 50 years or having multiple first-degree relatives affected regardless of their age. When none of the first-degree relatives had experienced a venous thrombosis, family history was defined as negative. The answer "I don't know" also indicated a negative family history.

ENVIRONMENTAL TRIGGERS

Environmental triggers were surgical treatment, injury (any self-reported injury, such as muscle ruptures or sprain), immobilization (plaster cast, extended bed rest at home for at least 4 days, or hospitalization) pregnancy or puerperium within 3 months before the index date, use of oral contraceptives or hormone therapy at the index date, and diagnosis of malignancy within 5 years before or within 6 months after the index date. The index date was defined as the date of diagnosis for patients and their partners and the date of completing the questionnaire for random controls.

GENETIC RISK FACTORS

Genetic risk factors were the factor V Leiden mutation, the prothrombin 20210A mutation, low antithrombin levels, low protein C levels, and low protein S levels. Because many mutations in the genes encoding antithrombin, protein C, and protein S may cause deficiency, protein levels served as a surrogate for genetic defects. A sample was classified as "low" when the protein level was below the reference value calculated in control subjects (geometric mean minus 2 SDs). For proteins C and S, the reference values were calculated excluding vitamin K antagonist users. In addition, we compared protein C levels with factor VII levels and protein S levels with factor II levels to discriminate between "isolated" low protein C or S levels and overall low coagulation factor levels. We calculated the expected protein C level by linear regression of protein C on factor VII and calculated the observed-over-expected ratio for protein C.[14] For protein S, the observed-over-expected ratio was calculated by regression on factor II. The observed protein C or S level was classified as "low" when both the absolute value and the observed-over-expected ratio were below the reference value calculated in control subjects (geometric mean minus 2 SDs). Specific reference values of protein C and protein S levels were calculated for vitamin K antagonist users and were included in sensitivity analyses; the ratios to factors VII and II are independent of vitamin K antagonist use.

For the present analysis, we selected participants who provided complete information about family history and environmental triggers and donated a blood sample. Among 3033 patients who completed the questionnaire, 2712 (89.4%) provided information about family history, and complete information about environmental triggers and a blood sample were available from 1959 patients (64.6%). In the control group, 4317 of 4887 participants (88.3%) provided information about family history, and 2438 (49.9%) provided complete information about environmental triggers and a blood sample.

During pregnancy and oral contraceptive use, protein S levels are reduced and cannot be used as an indicator of a genetic defect of protein S. We therefore excluded women who were pregnant (0 participants) or used oral contraceptives (146 patients [7.5%] and 259 control subjects [10.6%]) at the time of the blood draw. We also excluded vitamin K antagonist users (208 patients [10.6%] and 20 control subjects [0.8%]) because protein C and protein S levels cannot be easily interpreted under these circumstances. After these exclusions, 1605 patients and 2159 control subjects remained in the analyses.

LABORATORY ANALYSIS

Collection and processing of blood samples, subsequent DNA isolation, and genotyping of factor V Leiden and the prothrombin 20210A mutation have been described previously.[15] Measurements of antithrombin and protein C levels were performed with a chromogenic assay, and factors II and VII level measurements were based on a mechanical clotting time assay. These measurements were performed on a STA-R coagulation analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnières, France). Total protein S levels were measured by an enzyme-linked immunosorbent assay (Diagnostica Stago). The mean intraassay and interassay coefficients of variation were 1.7% and 2.6%, respectively, for antithrombin, 1.4% and 3.5% for protein C, 2.7% and 4.2% for factor II, 3.4% and 4.0% for factor VII, and 5.0% and 3.5% for protein S.

STATISTICAL ANALYSIS

Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to estimate the relative risk of venous thrombosis associated with a positive family history. Using the group with a negative family history as reference, ORs were calculated for having any affected first-degree relative (with the exception of offspring), having a first-degree relative affected before age 50 years, and having multiple affected first-degree relatives. Adjustment for age (continuous) and sex was performed by logistic regression. Subgroup analyses were performed within strata of known risk factors and within 10-year age categories. We calculated the positive predictive value and sensitivity of family history to identify genetic risk factors. For the positive predictive value and sensitivity estimates, binomial 95% CIs were calculated using the normal approximation.

Table 1. Distribution of Age, Sex, and Individual Risk Factors[a]

	Patients With Venous Thrombosis (n=1605)	Control Subjects (n=2159)
Median age (5th-95th percentile), y	50 (27-68)	51 (28-67)
Male sex	772 (48.1)	1150 (53.3)
Type of VT		
DVT	949 (59.1)	NA
PE	510 (31.8)	NA
DVT and PE	146 (9.1)	NA
All environmental risk factors	1086 (67.7)	425 (19.7)
Surgery	276 (17.2)	63 (2.9)
Injury	266 (16.6)	141 (6.5)
Immobilization	496 (30.9)	136 (6.3)
Pregnancy/puerperium[b]	68 (4.2)	21 (0.9)
Oral contraceptives/HT[b]	456 (28.4)	108 (5.0)
Malignancy	100 (6.2)	48 (2.2)
Any genetic risk factor	393 (24.5)	243 (11.3)
Factor V Leiden mutation	246 (15.3)	102 (4.7)
Prothrombin 20210A mutation	73 (4.5)	37 (1.7)
Low antithrombin level	39 (2.4)	56 (2.6)
Low protein C level	35 (2.2)	23 (1.1)
Low protein S level	26 (1.6)	36 (1.7)

Abbreviations: DVT; deep venous thrombosis; HT, hormone therapy; NA, not applicable; PE, pulmonary embolism; VT, venous thrombosis.

[a] Data are given as number (percentage) of participants unless otherwise indicated.

[b] The pregnancy and hormone use risk factor groups included women only, but the percentages are of the total study group, including men and women.

Table 2. First-Degree Family History of Venous Thrombosis

	No. (%) of Participants		
Family History	Patients With Venous Thrombosis (n=1605)	Control Subjects (n=2159)	Odds Ratio (95% Confidence Interval)
Negative	1100 (68.5)	1786 (82.7)	1 [Reference]
Positive			
Any relative	505 (31.5)	373 (17.3)	2.2 (1.9-2.6)
Relative <50 y	240 (15.0)	144 (6.7)	2.7 (2.2-3.4)
>1 Relative	97 (6.0)	40 (1.9)	3.9 (2.7-5.7)

RESULTS

Median age and distributions of sex and individual risk factors among the 1605 patients and 2159 control subjects are listed in **Table 1**. Family history of venous thrombosis was positive for 505 patients (31.5%) and 373 control subjects (17.3%) (**Table 2**). The overall OR of a positive relative to a negative family history was 2.2 (95% CI, 1.9-2.6). The association was stronger when only family members who had venous thrombosis before age 50 years were considered positive (OR, 2.7 [95% CI, 2.2-3.4]) or when several relatives were affected (3.9 [2.7-5.7]). The OR for venous thrombosis when several relatives were affected, at least 1 of them before age 50 years, was 4.4 (95% CI, 2.8-6.9[data not shown in the tables]). The median (25th-75th percentile) number of parents and siblings reported in the questionnaire was 5 (3-7) in the patient group and 5 (3-6) in the control group.

In 150 of 505 patients (29.7%) with a positive family history, a genetic risk factor was identified. A higher number of affected relatives and a younger age at which the relative was affected increased the chance of finding a genetic risk factor, up to 36.1% for patients with several affected relatives (positive predictive value; **Table 3**). The negative predictive value, ie, the chance that known genetic risk factors are indeed absent when the family history is negative, was 77.9%. This indicates that 22.1% of patients were thrombophilia carriers despite a negative family history. In the control group, genetic risk factors were less prevalent than among patients, and the positive predictive values were lower. The receiver operating characteristic curve for any relative affected, which represents the accuracy of family history in identifying genetic risk factors, had an area under the curve of only 54.4% in patients and 52.6% in the control group. When we took the presence of a genetic risk factor as the starting point, a positive family history was reported by 38.2% of patient carriers and by 21.8% of control carriers (sensitivity; Table 3). Thus, most thrombophilia carriers did not have affected relatives.

To study the value of family history as a risk indicator when known risk factors have been measured, we grouped patients and control subjects according to type of risk factor identified: none, environmental, genetic, or both (**Table 4**). In all strata, patients more frequently reported having affected relatives than did control subjects. Therefore, family history is a risk indicator regardless of the presence of known risk factors.

The relative risk associated with a positive family history was of similar magnitude as the risk associated with a genetic risk factor. In the absence of environmental triggers, the ORs were 2.5 for family history and 2.3 for a genetic risk factor. In the presence of environmental triggers, the ORs were 16.4 for family history and 21.2 for a genetic risk factor. The OR increased with the number of risk factors identified; for those with a combination of any genetic and acquired factor, the risk was about 60-fold higher than for those with no known risk factor and a negative family history.

To rule out specific combinations or the number of genetic risk factors as the cause of a higher prevalence of positive family histories in patients with genetic risk factors, we stratified this group by the specific genetic risk factors. In the group that carried factor V Leiden but no other genetic risk factor (40 patients and 22 control subjects), a positive family history further increased the risk of venous thrombosis; factor V Leiden carriers with a positive family history had a 2.9-fold higher risk than did factor V Leiden carriers with a negative family history (95% CI, 1.5-5.7). When an affected relative was younger than 50 years, this OR was 5.4 (95% CI, 2.0-14.6), and when at least 2 relatives were affected, the OR was 17.8 (2.2-143.1). The other strata of specific genetic risk factors included fewer patients and control subjects, thereby precluding meaningful analysis.

Genetic risk factors might play the most prominent role at a young age, when environmental triggers are less prevalent. We therefore calculated ORs for family his-

Table 3. Family History of Venous Thrombosis and Prevalence of Genetic Risk Factors

Family History[a]	Known Genetic Risk Factor[b]		Predictive Value, % (95% CI)	Sensitivity, % (95% CI)
	Yes	No		
Patients With Venous Thrombosis (n=1605)				
Negative	243	857	78 (75 to 80)	NA
Positive				
Any relative	150	355	30 (26 to 34)	38 (33 to 43)
Relative <50 y	80	160	33 (27 to 39)	20 (15 to 26)
>1 Relative	35	62	36 (27 to 46)	9 (4 to 14)
Control Subjects (n=2159)				
Negative	190	1596	89 (88 to 91)	NA
Positive				
Any relative	53	320	14 (11 to 18)	22 (17 to 27)
Relative <50	19	125	13 (8 to 19)	8 (2 to 14)
>1 Relative	9	31	23 (10 to 35)	4 (–3 to 11)

Abbreviations: CI, confidence interval; NA, not applicable.
[a]History of venous thrombosis among parents, brothers, and sisters.
[b]Low levels of antithrombin, protein C, or protein S; factor V Leiden mutation; or prothrombin 20210A mutation. Data are given as number of participants.

Table 4. Family History of Venous Thrombosis in Strata of Known Risk Factors

Family History[a]	No. (%)		Odds Ratio (95% CI)	
	Patients With Venous Thrombosis	Control Subjects	Per Stratum of Type of Risk Factor Identified	Relative to the Group With No Known Risk Factors and Negative Family History
No Known Risk Factors				
All	n=389	n=1538	. . .	. . .
Negative	261 (67.1)	1286 (83.6)	1 [Reference]	1 [Reference]
Positive				
Any relative	128 (32.9)	252 (16.4)	2.5 (1.9-3.2)	2.5 (1.9-3.2)
Relative <50 y	53 (13.6)	98 (6.4)	2.7 (1.9-3.8)	2.7 (1.9-3.8)
>1 Relative	23 (5.9)	27 (1.8)	4.2 (2.4-7.4)	4.2 (2.4-7.4)
Environmental Risk Factors Only[b]				
All	n=823	n=378	. . .	. . .
Negative	596 (72.4)	310 (82.0)	1 [Reference]	9.5 (7.8-11.5)
Positive				
Any relative	227 (27.6)	68 (18.0)	1.7 (1.3-2.4)	16.4 (12.2-22.2)
Relative <50 y	107 (13.0)	27 (7.1)	2.1 (1.3-3.2)	19.5 (12.5-30.4)
>1 Relative	39 (4.7)	4 (1.1)	5.1 (1.8-14.3)	48.0 (17.0-135.6)
Genetic Factors Only[c]				
All	n=130	n=196	. . .	. . .
Negative	71 (54.6)	150 (76.5)	1 [Reference]	2.3 (1.7-3.2)
Positive				
Any relative	59 (45.4)	46 (23.5)	2.7 (1.7-4.4)	6.3 (4.2-9.5)
Relative <50 y	33 (25.4)	15 (7.7)	4.6 (2.4-9.1)	10.8 (5.8-20.2)
>1 Relative	14 (10.8)	6 (3.1)	4.9 (1.8-13.4)	11.5 (4.4-30.2)
Environmental and Genetic Factors				
All	n=263	n=47	. . .	. . .
Negative	172 (65.4)	40 (85.1)	1 [Reference]	21.2 (14.7-30.6)
Positive				
Any relative	91 (34.6)	7 (14.9)	3.0 (1.3-7.0)	64.1 (29.4-139.8)
Relative <50 y	47 (17.9)	4 (8.5)	2.7 (0.9-8.0)	57.9 (20.7-162.1)
>1 Relative	21 (8.0)	3 (6.4)	1.6 (0.5-5.7)	34.5 (10.2-116.5)

Abbreviation: CI, confidence interval.
[a]History of venous thrombosis among parents, brothers, and sisters.
[b]Surgery, injury, immobilization, and pregnancy or puerperium within 3 months before the index date, use of oral contraceptives or hormone therapy at the index date, and diagnosis of malignancy within 5 years before or within 6 months after the index date.
[c]Low levels of antithrombin, protein C, or protein S; factor V Leiden mutation; or prothrombin 20210A mutation.

tory per 10-year age category. Family history was associated with the risk of venous thrombosis in all age groups. The relative risk slightly decreased with age; the ORs (95% CIs) for any relative affected were 3.2 (1.7-6.0) at age 18 to 29 years, 2.4 (1.6-3.6) at age 30 to 39 years, 2.1 (1.5-2.8) at age 40 to 49 years, 2.1 (1.6-2.8) at age 50 to 59

years, and 2.2 (1.6-3.1) at age 60 to 69 years. Because thrombotic events in a family accumulate during life and the risk of venous thrombosis increases with age, we further studied whether age could have confounded our results. Adjustment for age did not change any of the estimates. We also adjusted for sex to assess the impact of possible associations between oral contraceptive use and family history, but again none of the estimates changed.

Relatives for whom the answer to the question about family history was "I don't know" were assumed to be negative for venous thrombosis. Among patients, 238 of 1605 (14.8%) had at least 1 relative with unknown venous thrombosis history when all other first-degree relatives were known to be negative (ie, family history assumed negative); among controls, 307 of 2159 (14.2%) answered "I don't know" for at least 1 relative. Excluding these participants from the analysis led to slightly higher risk estimates for the family history.

All analyses were repeated including vitamin K antagonist users and oral contraceptive users. Including these users influenced the family history distributions by only a few percentage points.

COMMENT

In a large population-based case-control study, we showed that a positive family history increased the risk of venous thrombosis more than 2-fold, regardless of the risk factors precipitating the thrombosis. A young age of the affected relative and, in particular, the number of affected relatives more strongly indicated a predisposition to develop venous thrombosis.

Family history and known genetic risk factors were poorly associated, as observed previously.[4-6,8,16] Both the positive predictive value and sensitivity of family history as a test for genetic risk factors were low, with receiver operating characteristic curves hardly different from a random distribution. The poor predictive value either implies the existence of unknown genetic risk factors or clustering through household effects.

Patients more frequently had a positive family history than did control subjects, even when known risk factors were similar. This indicates that an unknown, probably genetic factor caused their disease in concert with the risk factor identified. These findings suggest that most genetic risk factors have low penetrance. Only when additional risk factors are present will venous thrombosis develop.[17,18] The search for novel genetic risk factors should not be limited to patients without known thrombophilia because genetic factors that interact with already known genetic risk factors might then not be found. Because most carriers of a single genetic risk factor have a negative family history, the sensitivity of family history in identifying a single genetic risk factor is low.

We selected low levels of antithrombin, protein C, and protein S; the factor V Leiden mutation; and the prothrombin 20210A mutation as genetic risk factors. These are clear and frequent genetic risk factors for venous thrombosis. Inclusion of more genetic risk factors will increase the positive predictive value at the cost of the negative predictive value, while sensitivity may remain low. More important, our study confirms that venous thrombosis is a multigene disorder. Family history will be a better surrogate for multiple genetic risk factors, including those yet unknown, than for single defects.

Relatives generally underreport disease in their families.[19-23] We believe that, in our study, family history may also have been underreported. The study does, however, correspond to clinical practice, in which physicians rely on the family history information given by their patient and confirmation of all relatives' disease status is not feasible. Alternatively, we might have overestimated the prevalence of positive family histories because individuals might be more prone to participate in a study of venous thrombosis when their family history is positive. As selection is most likely in the control group, we might have underestimated the effect of family history.

Antithrombin, protein C, and protein S levels were determined from 1 blood sample. In a clinical setting, low protein levels are confirmed by a second measurement before a patient is diagnosed as deficient. A previous study among patients with venous thrombosis and control subjects[24] reported that 5 of 20 patients (25.0%) who initially had antithrombin levels below the lower limit of normal had low levels at a second measurement. Confirmation of low protein C levels occurred in 15 of 22 patients (68.2%), and confirmation of low protein S levels in 5 of 8 patients (62.5%). Confirmation occurred less frequently in control subjects. We acknowledge that the number of individuals with truly low levels of antithrombin, protein C, and protein S will be lower than that presented here.

We studied whether family history is of additional value in predicting an individual's risk of venous thrombosis once a genetic risk factor has been identified. We could also reverse the question and ask whether genetic testing provides additional prognostic value once the family history has been determined. This could guide decisions on starting oral contraceptive use or taking preventive measures during immobilization. Table 4 shows that environmental risk factors together with a positive family history strongly increase the risk of venous thrombosis. In the absence of a known genetic risk factor, the risk is already increased more than 15-fold. Genetic testing to identify additional risk would then not seem useful. Moreover, the positive family history could well reflect unknown genetic risk factors. When the family history is negative, an environmental risk factor would increase the risk about 10-fold to 20-fold, depending on the identification of a genetic risk factor. Given the low chance of finding a genetic risk factor when the family history is negative, genetic testing does not seem to be cost-effective in this situation.

It is important to note that the results from the present study apply to the risk of a first venous thrombosis and may not be applicable to risk of recurrent venous thrombosis. In fact, previous studies have shown that neither genetic risk factors nor family history are predictive for recurrent venous thrombosis.[25,26]

We conclude that family history is a risk indicator for a first venous thrombosis, even when a genetic risk factor has been identified. In clinical practice, family history may be more useful for risk assessment than thrombophilia tests. A positive family history represents

increased susceptibility in addition to the risk caused by known genetic and environmental factors. This additional risk is due to unknown or unmeasured risk factors.

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