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The Incidence of Venous Thromboembolism in Family Members of Patients with Factor V Leiden Mutation and Venous Thrombosis

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Background: The factor V Leiden mutation is a genetic defect associated with an increased incidence of venous thromboembolism. When the incidence of venous thromboembolism in relatives of patients known to have the mutation outweighs the disadvantages of prophylactic strategies, family screening may be necessary.

Objective: To determine the incidence of venous thromboembolism in first-degree relatives of symptomatic carriers of the factor V Leiden mutation.

Design: Retrospective blinded study.

Setting: University hospitals.

Participants: 437 first-degree relatives of 112 heterozygous propositi and 30 relatives of 6 homozygous propositi.

Measurements: Before DNA testing, information on previous venous thromboembolism and concomitant risk factors was obtained. Relatives with and without the FV: Q⁵⁰⁶ mutation were compared.

Results: The annual incidence of thromboembolism in relatives of heterozygous propositi was 0.45% (95% CI, 0.28% to 0.61%) in those with the mutation and 0.10% (CI, 0.02% to 0.19%) in those without the mutation (relative risk, 4.2 [CI, 1.8 to 9.9]). Among carriers, the incidence increased from 0.25% (CI, 0.12% to 0.49%) in the 15- to 30-year-old age group to 1.1% (CI, 0.24% to 3.33%) in persons older than 60 years of age. Half of the episodes of venous thromboembolism occurred spontaneously, 20% were related to surgery, and 30% were associated with pregnancy or use of oral contraceptives.

Conclusions: The observed low annual risk for venous thromboembolism in persons carrying the factor V Leiden mutation does not seem to outweigh the risks for bleeding associated with coumarin prophylaxis or justify discouragement of the use of oral contraceptives. A general policy of screening the families of all patients with the factor V Leiden mutation does not seem to be indicated. The observations in this moderate-size, retrospective study need to be confirmed by prospective follow-up studies.

Until recently, the cause of venous thromboembolism remained obscure in most patients with the disease. Isolated deficiencies of physiologic inhibitors of the coagulation system, such as antithrombin, protein C, and protein S, could be detected in only about 8% of consecutive patients with documented venous thromboembolism (1). In 1994, resistance to activated protein C was reported as a new risk factor for venous thromboembolism (2). Researchers then found that a single point mutation (G1691A) in the factor V gene at the major cleavage site of activated protein C causes this phenomenon (also called factor V Leiden mutation) (3-5). This mutation is now considered the most common genetic defect leading to an increased risk for venous thromboembolism, with a prevalence as high as 20% to 50% in patients with thrombosis (2, 6). The overall prevalence in western populations has been estimated to be approximately 5% (7). Earlier studies have shown that the relative risk for venous thromboembolism in heterozygous carriers of the factor V Leiden mutation compared with healthy controls is approximately 7 (2, 6). This value may increase to 30 when other risk factors, such as exposure to oral contraceptives, are simultaneously present (8). However, recent studies found a lower relative risk, probably as a result of differences in patient selection (9, 10).

Given that half of the relatives of each patient with thrombosis and the factor V Leiden mutation will carry the same defect (because of the autosomal dominant inheritance pattern of the affected allele), a clinical question emerges. Should families of patients known to have the mutation be actively screened for the presence of the mutation so that the institution of prophylactic anticoagulant strategies, either permanent or during high-risk situations, can be considered?

For any genetic disorder, the benefits of early detection and appropriate preventive measures need to be weighed against the disadvantages of screening asymptomatic persons and labeling them as hav-

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ing a disease. The primary benefit of screening is the ability to prevent disease or treat it at an earlier stage. Disadvantages include the psychological stress induced among carriers of the genetic defect, the risks associated with the prevention or treatment of the disorder, and the economic consequences. To rationally decide whether the benefits of screening outweigh the disadvantages, it is crucial to know the absolute risk for the clinical expression of the disorder and its potentiating factors. If this information is available for the factor V Leiden mutation, it may become feasible to weigh the risk for venous thromboembolism against the known benefits and hazards of anticoagulant prophylaxis. We therefore investigated 467 first-degree relatives of 118 consecutive patients seen at our institutions with documented venous thromboembolism and the factor V Leiden mutation. For all relatives, we obtained a medical history with emphasis on previous episodes of venous thromboembolism and exposure to such risk factors as surgery, immobilization, pregnancy, and use of oral contraceptives. We then determined the presence or absence of the mutation and compared the findings in family members who have the mutation with those in family members who have a normal genotype.

Methods

Patients and Study Design

In the participating centers, all patients with a proven episode of venous thromboembolism are tested for the presence of an underlying coagulation disorder. A total of 118 patients with the factor V Leiden mutation were invited to participate in this project and were considered *propositi*. Of these *propositi*, 112 were heterozygous carriers of the mutation (36 men and 76 women; mean age at time of first thromboembolic event, 36 years) and 6 were homozygous carriers (2 men and 4 women; mean age at time of first thromboembolic event, 29 years).

All living first-degree relatives (parents, siblings, and children older than 15 years of age) of the *propositi*, identified through pedigree analysis, formed the study cohort. Incidence of venous thromboembolism and exposure to established risk factors in the first-degree family members of heterozygous and homozygous *propositi* were analyzed separately.

After reading information about the aims and design of the study, each family member was interviewed by one of the investigators using a standardized medical history form. Detailed information was obtained about previous episodes of venous thromboembolism, surgical interventions, trauma, periods of immobilization, and prophylactic or therapeutic

use of anticoagulant drugs. For women, the use of oral contraceptives and the obstetric history were documented. At the end of the outpatient visit, blood was obtained for determination of mutation status. Mutation status (normal, heterozygous, or homozygous) was determined by using a polymerase chain reaction-based assay, as described previously (5). The institutional review boards of the participating centers approved the study, and all participants gave informed consent.

Definitions

A previous episode of venous thromboembolism was considered to have occurred if it had been confirmed by venography, ultrasonography, impedance plethysmography, ventilation-perfusion lung scanning, or pulmonary angiography. When no objective testing had been done but the patient had received full-dose intravenous heparin or oral anticoagulants for at least 3 months, he or she was considered to have previously had venous thromboembolism and was included in the analysis. For this classification, the patients' charts were reviewed.

Episodes of increased risk for venous thromboembolism included pregnancy, surgery, trauma, immobilization for more than 7 days, and use of oral contraceptives. An episode of venous thromboembolism was considered to be related to such a situation when it occurred within 3 months of the last day of that situation. Observed years are all years since the age of 15 years until inclusion in the study or until the date of the first venous thromboembolic event; this time period was chosen because it was considered to reflect the duration of exposure to the risk for venous thromboembolism. The age of 15 years was chosen because venous thrombosis rarely occurs in children. The information from the medical history (and, if necessary, from other sources) was classified without knowledge of mutation status.

Statistical Analysis

The overall and age-specific annual incidence of a first episode of venous thromboembolism was calculated in relatives with and those without the factor V Leiden mutation by dividing the number of symptomatic family members by the observed years. The relative risk for the development of a first episode of venous thromboembolism (adjusted for extremes if necessary) was calculated by dividing the incidence of venous thrombosis in family members with the mutation by the incidence in family members with the normal genotype. The 95% CIs were calculated according to normal approximation of the binomial distribution. We calculated a Kaplan-Meier estimate for a visual assessment of event-free survival in relatives with and those without the mutation. The relative risk (and its mid-*P*-corrected

95% CI) for pregnancy- and surgery-related venous thromboembolism was calculated by using a Cox model. For this purpose, a risk period was considered as a unit of time, and persons who had not had a thromboembolic event by the end of their last risk period were considered to be censored. If a relative had had an episode of venous thromboembolism, all subsequent high-risk situations were excluded from the analysis to avoid enhancing risk and because anticoagulant prophylaxis is often given after such an episode.

Results

The pedigrees of the 118 probands with documented venous thromboembolism and the factor V Leiden mutation revealed 689 first-degree family members older than 15 years of age. Of these, 127 had died before the study began. Of these deceased relatives, 116 were parents of the probands (mean age of probands at the time of study entry, 43 years [range, 17 to 89 years]) or siblings of elderly probands. For 9 other relatives, the cause of death was reported and was not related to venous thromboembolism. For 1 relative, neither the age at time of death nor the cause of death was known. Two sudden deaths, occurring at 28 years of age (brother of a proband) and 55 years of age (mother of a proband), were reported. Twenty-one relatives were unavailable because they lived outside of the Netherlands. Another 74 relatives could not participate for various reasons, including reluctance to undergo assessment of genetic disorders, inability to give consent, and the presence of terminal diseases. Thus, 467 first-degree family members were included in the study (response rate of living family members, 83%; overall response rate, 68%). Of the 467 family members, 437 were related to the 112 heterozygous probands; 30 family members were related to the 6 homozygous probands.

Of the 437 relatives of heterozygous probands, approximately half carried the mutation (Table 1).

Table 1. Clinical Characteristics and Frequency of a First Episode of Venous Thromboembolism in 437 First-Degree Relatives of 112 Heterozygous Probands

Variable	Relatives without Factor V Leiden Mutation (n = 201 [46%])	Relatives with Factor V Leiden Mutation (n = 236 [54%])
Men, n (%)	94 (47)	105 (44)
Women, n (%)	107 (53)	131 (56)
Mean age (range), y	44 (16–84)	45 (16–88)
Persons with venous thromboembolism, n	6	29
Observation period, y	5716	6524
Annual incidence (95% CI), %	0.10 (0.02–0.19)	0.45 (0.28–0.61)
Relative risk (95% CI)	1.0	4.2 (1.8–9.9)

Of the 236 family members with the mutation, 7 were found to be homozygotes. Six relatives without the mutation and 29 relatives with the mutation reported having had venous thromboembolism. In the group without the mutation, 1 person had pulmonary embolism, 3 had deep venous thrombosis of the popliteal vein, and 2 had thrombosis that extended into the femoral vein. In the group with the mutation, these figures were 6, 13, and 10, respectively. The absolute annual incidence of a first episode of venous thromboembolism was 0.10% (95% CI, 0.02% to 0.19%) in the group with a normal genotype and 0.45% (CI, 0.28% to 0.61%) in the group with the mutation. Thus, the overall relative risk for a first episode of venous thromboembolism in family members with the mutation was 4.2 (CI, 1.8 to 9.9). Table 2 shows the age-specific annual incidence of a first episode of thrombosis in relatives with and those without the mutation; the absolute annual incidence in the youngest age group with the mutation was 0.25% (CI, 0.12% to 0.49%). This rate gradually increased to 1.1% (CI, 0.24% to 3.33%) in affected relatives older than 60 years of age. The Figure shows the thrombosis-free survival curves in family members with and those without the mutation.

In the family members with a normal genotype, 4

Table 2. Age-Specific Annual Incidence of a First Episode of Venous Thromboembolism in 437 First-Degree Relatives of 112 Heterozygous Probands*

Variable	Age Group			
	15–30 y	30–45 y	45–60 y	>60 y
Factor V Leiden mutation absent				
First episode of VTE, n	0	2	3	1
Observation period, y	2757	1848	868	243
Annual incidence (95% CI), %	0.0 (0–0.13)	0.11 (0.02–0.39)	0.35 (0.07–1.01)	0.41 (0.01–2.28)
Factor V Leiden mutation present				
First episode of VTE, n	8	10	8	3
Observation period, y	3149	2133	981	261
Annual incidence (95% CI), %	0.25 (0.12–0.49)	0.47 (0.23–0.86)	0.82 (0.35–1.61)	1.1 (0.24–3.33)
Relative risk (95% CI)	≈15 (0.9–257)	4.3 (1.0–20)	2.4 (0.6–8.9)	2.8 (0.3–27)

* VTE = venous thromboembolism.

Figure. Thromboembolic event-free survival in 437 first-degree relatives of 112 heterozygous probands with the factor V Leiden mutation. The black lines represent relatives without the mutation; the dashed lines represent relatives with the mutation.

of the 6 persons with thrombosis were men; in the relatives with the mutation, two thirds of those with thrombosis were women (11 of 29 persons). Of the 29 relatives with venous thrombosis and the mutation, 3 were homozygotes. All 6 persons in the group without the factor V Leiden mutation had a single episode of thrombosis, whereas a second episode of venous thromboembolism occurred in 8 of the 29 relatives with the mutation. Five of these episodes occurred spontaneously, 1 was related to surgery, and 2 were related to pregnancy. In 1 relative, who was a homozygote, 2 recurrent episodes of pulmonary embolism occurred spontaneously.

Of the 30 family members of 6 homozygous probands, 2 had a normal genotype and 28 carried the factor V Leiden mutation (**Table 3**). Four of the 28 relatives with the mutation were found to be homozygotes. In the 28 relatives with the mutation, the absolute annual incidence of venous thromboembolism was 0.40% (CI, 0.01% to 0.90%). Of the 3 relatives with thrombosis and the mutation, 1 was a homozygote.

A further analysis of the association with established risk factors was limited to the 437 first-degree family members of the 112 heterozygous probands. Mean age at the time of the first episode was 41 years (range, 17 to 79 years) in the group with the mutation and 48 years (range, 35 to 61 years) in the group without the mutation. In both groups, half of the thrombotic episodes occurred spontaneously (**Table 4**). Among women who used oral contraceptives, the relative risk for venous thromboembolism was 3.3 in those who had the factor V Leiden mutation compared with those who did not have the mutation. The absolute annual incidence of venous thrombosis among women who had the mutation and used oral contraceptives was low (0.48% [CI, 0.10% to 1.40%]). No pregnancy-related episodes of venous thromboembolism occurred in the group

with the normal genotype; in the group with the mutation, 5 of 235 pregnancies were complicated by venous thromboembolism. Four of these episodes occurred within 6 weeks postpartum, and 1 occurred a few days before delivery. In the group without the mutation, 2 episodes of venous thromboembolism were related to surgery, immobilization, or trauma; in the group with the mutation, 6 episodes (including 2 for which prophylactic anticoagulants were used) were related to these risk factors (relative risk, 2.4 [CI, 0.5 to 12]).

Discussion

Our findings indicate that a first-degree relative of a symptomatic heterozygous proband has an absolute annual risk for a first episode of venous thromboembolism of only 0.45% (CI, 0.28% to 0.61%). This is approximately fourfold higher than the risk in nonaffected family members (**Table 1**). The relative risk between carriers and noncarriers of the factor V Leiden mutation is higher in the younger age group (15 to 30 years), probably because of pregnancies and exposure to oral contraceptives in women. However, it is important to note that the absolute risk in this age group is low compared with that in the older age groups who carry and do not carry the mutation (**Table 2**). The observed annual incidence in the relatives with a normal genotype is similar to the reported population risk for venous thromboembolism (11). The overall relative risk found in our study, which included relatives of unselected probands, seems to be lower than that seen in case-control studies (2, 6) but is similar to that observed in the large prospective Physicians' Health Study (9). We also studied the absolute annual incidence of a first episode of venous thrombosis in the relatives of six symptomatic patients known to be homozygous for the mutation. Although we could study only 30 first-degree relatives, the observed absolute annual incidence

Table 3. Clinical Characteristics and Frequency of a First Episode of Venous Thromboembolism in 30 First-Degree Relatives of 6 Homozygous Probands

Variable	Relatives without Factor V Leiden Mutation (n = 2 [7%])	Relatives with Factor V Leiden Mutation (n = 28 [93%])
Men, n (%)	0 (0)	12 (43)
Women, n (%)	2 (100)	16 (57)
Mean age (range), y	33 (22–43)	43 (15–76)
Persons with venous thromboembolism, n	0	3
Observation period, y	35	750
Annual incidence (95% CI), %	0.0 (0.0–10.0)	0.40 (0.01–0.90)
Relative risk (95% CI)	1.0	3.0 (0.2–0.9)

(0.40% [CI, 0.01% to 0.90%]) did not differ from that seen in the relatives of the heterozygous propositi (Table 3).

When the first thromboembolic episodes in the relatives with the mutation were analyzed in relation to precipitating factors, we found that approximately 50% of the episodes occurred spontaneously, whereas only 20% were related to surgery, trauma, or immobilization (Table 4). Most of these latter cases occurred when routine prophylaxis of thrombosis was not common practice. The remaining episodes of venous thromboembolism in these affected family members were related to either oral contraceptive use or pregnancy.

Several methodologic aspects of our study warrant comment. First, our study had a retrospective design. To limit the potential for bias, we used a standardized history form for all study participants, applied strict criteria defined a priori for previous episodes of venous thromboembolism, and obtained all information without knowledge of DNA test results. Second, although the response rate of the available family members was high (83%), we could not investigate the deceased relatives. However, it is unlikely that the incidences we observed are underestimated by early deaths in carriers of the factor V Leiden mutation that were caused by venous thromboembolism. It has previously been documented that the life expectancy of persons with other hereditary defects causing familial thrombophilia is normal (12, 13), and there is no reason to believe that the situation for the factor V Leiden mutation is different. Moreover, if we contemplate the following worst-case scenario, in which the factor V Leiden mutation would have been present in two thirds of the deceased family members (and assuming that the life expectancy of these relatives would be shortened to 65 years and that 25% of these carriers would have had their first episode of venous thromboembolism by the age of 40 years), the overall annual incidence increases only from 0.45% to 0.5%. Although the inability to include deceased relatives is an important limitation of our retrospective study, this worst-case scenario indicates that this limitation does not materially affect the observed incidence. On the other hand, the observed absolute risk for thromboembolism in the first-degree relatives in our study may be slightly overestimated. Although the criteria used to classify previous episodes of venous thromboembolism have been shown to be accurate, the inclusion of patients with clinically diagnosed episodes of previous venous thromboembolism followed by anticoagulant treatment probably inflates the observed absolute annual incidence (14). Thus, we are confident that our estimation of the annual risk for venous thromboembolism in carriers of the mutation is valid.

Table 4. Relation of First Episodes of Venous Thromboembolism and Established Risk Factors in 437 First-Degree Relatives of 112 Heterozygous Propositi*

Variable	Relatives without Factor V Leiden Mutation (n = 6)	Relatives with Factor V Leiden Mutation (n = 29)
Spontaneous VTE, n (%)†	3 (50)	15 (52)
VTE associated with oral contraceptive use, n†	1	3
Duration of use, y	677	624
Annual incidence (95% CI), %	0.15 (0.01–0.82)	0.48 (0.10–1.40)
Relative risk (95% CI)	1.0	3.3 (0.3–31)
Pregnancy-related VTE, n†	0	5
Episodes, n	188	235
Annual incidence (95% CI), %	0 (0.00–1.94)	2.1 (0.69–4.90)
VTE associated with surgery, trauma, or immobilization, n†	2	6
Episodes, n	262	325
Annual incidence (95% CI), %	0.7 (0.09–2.73)	1.8 (0.68–4.00)
Relative risk (95% CI)	1.0	2.4 (0.5–12)

* VTE = venous thromboembolism.

† Values are the number of patients.

What are the implications of our findings for actively identifying nonsymptomatic carriers of the mutation? For these persons, two prophylactic strategies are available in theory—the institution of life-long coumarin treatment or anticoagulant prophylaxis limited to high-risk situations. Given the low risk for thrombosis in carriers of the mutation and the known risk for major bleeding associated with therapeutic dosages of coumarin (2% to 10% per year) (15, 16), the first strategy does not seem to be an option and will probably do more harm than good. In considering the other strategy, it should be realized that half of the episodes of venous thromboembolism will not be prevented because they occur spontaneously. In addition, most of the thromboembolic complications occurring after surgery, trauma, or immobilization that we noted in our study occurred when routine thrombosis prophylaxis was not commonly used. It is plausible that the now-standard heparin prophylaxis will prevent most of these postoperative thrombi. Thus, family screening would not lead to a prophylactic approach in carriers of the mutation during high-risk situations that is different from common practice. A possible exception to this reasoning may be families with an extraordinary history of fatal, recurrent venous thromboembolism that occurred at a young age in several family members.

The appropriate approach with respect to screening for two other high-risk situations (pregnancy and oral contraceptive use) is more complex. In our study, approximately 2% of pregnancies in carriers were complicated by venous thromboembolism. This rate is 5- to 10-fold higher than the reported incidence of pregnancy-related thrombosis in the general population (11, 17, 18). To reduce this rela-

tively high incidence of thrombosis in carriers of the mutation, prophylactic use of low-molecular-weight heparin should begin during the puerperium and probably also during the last trimester, as has been suggested for other hereditary thrombophilic defects (18). Such a strategy, however, with its inherent inconvenience and risks for bleeding, osteoporosis, and thrombocytopenia, will then be used unnecessarily in 980 of 1000 pregnant carriers of the mutation. It is therefore questionable whether identifying asymptomatic carriers of the factor V Leiden mutation before they intend to become pregnant is desirable. Should female family members who are beginning to use oral contraceptives be screened for the presence of the mutation in order to discourage the use of oral contraceptives in those with the mutation? Our results indicate that to prevent three episodes of venous thromboembolism by family screening, 1000 young women with the mutation would have to be discouraged from using oral contraceptives, without knowing the scope of morbidity that results from such advice.

On the basis of these considerations and our data (and in contrast to suggestions in other papers [19, 20]), we conclude that no major benefit is to be expected from a general policy of screening the relatives of all patients with venous thromboembolism and the factor V Leiden mutation. Our findings do not support the usefulness of identifying asymptomatic carriers because this information will not have consequences for the prophylaxis of thrombosis during surgery or immobilization or for the use of oral contraceptives and prophylaxis during pregnancy and puerperium. Advice about screening might be different for families with an unusual tendency for recurrent venous thromboembolism at young age. In these families, knowledge of the mutation status may be useful in counseling women who are considering the use of oral contraceptives or who intend to become pregnant. This conclusion is in agreement with that of another recent analysis (21).

In conclusion, affected first-degree relatives of patients with thrombosis and factor V Leiden mutation had a low annual risk for a first episode of venous thromboembolism (0.45%). This conclusion is based on a moderate-size, retrospective study with some limitations; prospective family studies should be done to confirm our findings and to identify the appropriate strategy in families that may benefit from screening.

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