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Minor Events and the Risk of Deep Venous Thrombosis

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Key words

Venous thromboembolism, epidemiology, travel, immobilisation, risk factors, factor V

Summary

Background Deep venous thrombosis is a common disease, with genetic and acquired risk factors Many patients have a history of minor events (short periods of immobilisation such as prolonged travel, short illness, minor surgery or injuries) before onset of venous thrombosis However, the role of these minor events has received little formal study Also, we do not know how minor events might interact with the presence of genetic prothrombotic defects (factor V Leiden mutation factor II mutation, protein C S and antithrombin deficiency) *Patients and Methods* On the basis of case-control data from a thrombosis service in the Netherlands we added a follow-up period for a case-cross-over analysis of minor events as risk factors, and a case only analysis for the interaction with factor V Leiden A total of 187 patients with first, objectively diagnosed venous thrombosis of the legs, aged 15-70, without underlying malignancies and without major acquired risk factors entered the study For the analysis of minor events in the case-cross-over analysis we used a matched odds ratio, in the case only analysis we used the multiplicative synergy index *Results* In 32 6% of the 187 patients with deep venous thrombosis who did not have major acquired risk factors, minor events were the only external risk factors Minor events increased the risk of thrombosis about 3-fold as estimated in the case-cross-over analysis (odds ratio 2 9, 95% confidence interval 1 5-5 4) The synergy index between minor events and factor V Leiden mutation in the case-only analysis was 0 7 (95% confidence interval 0 3-1 5) Therefore, persons with factor V Leiden mutation who experience a minor event will have an estimated risk increase of about 17-fold, which exceeds the sum of the individual risk factors *Conclusions* Minor events are likely to play an important role in the development of deep venous thrombosis, especially in the presence of genetic prothrombotic conditions

Introduction

The incidence of deep venous thrombosis (DVT) in the general population is estimated to be 1 per 1000 per year Hereditary coagulation defects that are associated with an increased risk are protein C, protein S, antithrombin deficiency, factor II (20210 G to A) mutation, and APC resistance (Factor V Leiden mutation) (1) Acquired conditions that promote DVT include prolonged immobilisation, major injuries and surgery The combination of acquired and hereditary risk factors may lead to the highest risks In a substantial number of patients the underlying cause remains unresolved, however

Many patients with DVT, when asked, have a recent history of minor events strain or minor injuries due to effort, short illness or short immobilisation while travelling Since the risk brought about by major surgery and trauma, plaster casts and prolonged immobilisation is substantial, minor illnesses and interventions might prove to be moderate risk factors Nevertheless, minor events have only received anecdotal attention in the literature and very little formal study except for (air) travel (2-4) Our study was performed to investigate the role of minor events in DVT, and their possible interaction with genetic prothrombotic defects We reanalysed data from the Leiden Thrombophilia Study (LETS) (5) in which minor events, generally occurring within two weeks before the DVT, had been noted in patient discharge letters Firstly, we performed a case cross-over study four years after the first venous thrombosis patients were asked again if they had experienced a minor event in a new and arbitrary two week period This permitted us to use the cases as their own controls Secondly we studied the synergy between minor events and factor V Leiden in a case only analysis

Methods

The present study was an extension of the Leiden Thrombophilia Study (LETS) (5) The LETS study was performed between 1988 and 1993 and was a population based case control study on hereditary venous thrombosis Patients were selected from the files of the anticoagulant clinics in Leiden Amsterdam and Rotterdam Patients with known malignant disorders were excluded In total 474 consecutive outpatients were included (median age 47) Patients were referred for diagnosis after a first objectively confirmed episode of DVT All patients were seen by one of the main investigators and completed a standard questionnaire Several major acquired thrombosis risk factors were recorded prolonged immobilisation surgery hospitalisation without surgery pregnancy and postpartum period Genetic and biochemical risk factors analysed initially or later on were factor V Leiden mutation factor II (20210 A/G) mutation and deficiency of protein C protein S or antithrombin

Although the LETS questionnaire did not include standard questions for minor events these were regularly mentioned as a possible causative factor Most records from the patients selected in Leiden contained both extra comments of the investigator and hospital discharge letters The records from Amsterdam and Rotterdam did not have this extra information from the discharge letters For our present study, therefore only the Leiden records were used

We selected patients without any major acquired risk factor, only patients without an event or patients with a minor event occurring within two weeks before the DVT were selected Minor events were defined as bed rest more than 12 h a day for two or more consecutive days heavy physical exertion minor trauma minor surgery or prolonged travel (by car bus or plane) leading to diminished or painful use of one of the extremities

Two separate analyses were performed Firstly to estimate the relative risk of the minor event itself we applied a case-crossover study, using the cases of this study as their own control This was accomplished during the follow-up of

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these patients, on average four years after the initial inclusion: patients were asked if a minor event had occurred in the arbitrary two weeks period before they had been approached for this follow-up The follow-up was by questionnaire, augmented by telephone inquiries: patients could indicate on the questionnaire whether any minor event had happened recently, and they were subsequently phoned to ask the details and time window of these minor events Of each patient we therefore knew not only whether he or she had experienced a minor event in the (approximately) two weeks before the DVT, but also in an arbitrary two week period at another time in their life This permits a matched case-control analysis to see how much more frequent such events are in the weeks preceding DVT than in another period in the same patients life

Secondly, the minor events preceding the original venous thrombosis were studied in their combination with the presence of factor V Leiden The extent of interaction between the exposure of minor events and the presence of Factor V Leiden on the risk for thrombosis was assessed by a case-only study (6, 7, 8) The case-only study relies on the assumption that the two factors of interest are independently distributed in the general population That is a reasonable assumption for genetic risk factors and minor events for minor events that precede a first DVT in a patient it is likely that their occurrence, i e whether or not the patient engaged in plane travel before a first DVT, was not influenced by the presence or absence of a hitherto unknown genetic factor (factor V Leiden and the prothrombin mutation was unknown at the time of our original investigation) DVT cases are divided into those with and without minor events The odds ratio of the factor V Leiden is then an estimate of the synergy index on the multiplicative scale This synergy index is the factor by which the joint relative risks of genetic defects and minor events have to be multiplied

Results

We included 271 patients from the Leiden part of the LETS study The male/female ratio was 120/151, with mean age at diagnosis of the thrombosis 42 years (range 15-69, SD 14) Of the 271 patients 84 were excluded because of pregnancy or postpartum, major operations, prolonged immobilisation (more than two weeks), or hospital stay for more than three days preceding their DVT

Of the remaining 187 patients, 61 had experienced minor events (32 6%), the other 126 patients had no recorded event Table 1 shows the male/female ratio, mean age and range of the cases with and without minor events

Table 2 summarises the characteristics of the minor events The majority was bed rest at home for various conditions, including minor injuries Travel and minor surgery had lesser contributions The median interval between the events and the thrombosis was 2 days (range 0-14) The median time of the duration of the minor event was 1 day (range 1-14 days)

Table 1 Sex and age characteristics of the 187 patients included in the study

	male:female	mean age ± SD	range
minor events (n= 61)	31 30	43 3 ±13 4	14 6-68 7
no minor events (n=126)	55 71	42 8 ± 14 6	15 3-67 3

Table 2 Characteristics of the minor events preceding DVT

Minor event	Patients	Remark
Travel	11	car 6, plane 3, bus 1, otherwise 1
Rest at home > 12 h	36	hernia 6, malaise 6, infection 2, trauma 10, heavy physical exertion 12
Minor surgery	14	arthroscopy 6, meniscectomy 2, excision ganglion/pin knee 2, excision exostosis 1, sclerosing of varices 1, coronary angiography 1, other 1

Table 3 Coagulation abnormalities at time of deep venous thrombosis

Coagulation abnormality	with minor event (n=61)	no event (n=126)
protein C	1	7
protein S	2	2
FV Leiden AG	9	22
FV Leiden AA	-	3
Factor II (20210 A)	-	6

Table 4 Results of the case cross-over study

Minor Events	present before DVT	absent before DVT	
present in recent period	9	12	21
absent in recent period	35	72	107
	44	84	128

Coagulation abnormalities are summarised in Table 3 In 12 of the 61 patients (20%) with a minor event, a hereditory abnormality of coagulation was found (9 patients had a factor V Leiden) In the patients without minor events, 40 of the 126 patients (30%) had a coagulation abnormality (25 factor V Leiden) Note that 3 patients who were homozygotes for factor V Leiden and most of the patients with a protein C deficiency were found in the patient group without minor events

The case-cross-over study that was performed at approximately four years after the initial event, during a follow-up investigation, is presented in Table 4 Of the 187 patients, 128 could be included Several reasons existed for the exclusion of the 59 patients, ranging from pregnancy, nontraceability major medical events or unwillingness to participate Of these 128 patients, 21 had experienced a minor event during the recent two week period preceding the time of follow-up The matched analysis of the presence or absence of minor events is presented in Table 4 The matched odds-ratio as an estimate of the relative risk, is 2 9 (confidence interval 1 55 4)

We can restrict the case-cross-over analysis in Table 4 to those without factor V Leiden, in order to measure the independent effect of minor events Twenty of the 128 patients carried factor V Leiden all were among those without a recent minor event (6 of 35 and 14 of 72) The matched odds ratio without these patients became 2 4, which is

Table 5 Characteristics of the minor events in case cross-over study

Recent minor event	Patients	Type of recent event (n=21)	Minor event at original DVT (n=9)
Travel	5	car 2	- plane 1
		plane 2	- car 1
		bus 1	
Rest at home > 12 h	15	hernia 3	- malaise 1
		malaise 5	- trauma 2
		infection 4	- heavy physical exertion 2
			- hernia 1
		trauma 3	
Minor surgery	1	other 1	- car 1

Table 6 Results of the case-only study

Minor events	FV Leiden +	FV Leiden -	
+	9	52	61
-	25	101	126
	34	153	187

sufficiently close to the overall estimate of 2 9, given the small numbers

The type of minor events during the more recent two week period is presented in Table 5, together with the original minor event of the same groups of patients Conspicuously absent from the list of recent minor events in comparison with the ones preceding DVT is minor surgery The relative risk for minor surgery would therefore be very high

The synergy index of the interaction between minor events and factor V Leiden was obtained by a case-only analysis on the original data of DVT i e , the minor events preceding DVT and factor V Leiden DNA determinations In an analysis on Table 6, the odds-ratio, estimating the synergy index, is 0 69 with a confidence interval of 0 31 5, which indicates the presence of an incomplete multiplicative effect of about 0 7

Discussion

Our results support the hypothesis that minor events play an important role in the cause of venous thrombosis To estimate the separate effect of minor events, we used a case-cross-over study in which the cases were their own controls Four years after the venous thrombosis, patients were asked again if they had experienced minor events in an arbitrary two-week period This yielded a close to 3-fold increase in risk of venous thrombosis after minor events In addition we calculated a synergy index of about 0 7 between small events and factor V Leiden If we take the independent risk elevation of factor V Leiden to be 8-fold this means that the overall relative risk of a minor event in a person who carries the factor V Leiden mutation will be 8 times 3 times 0 7, which amounts to a relative risk of about 17 That joint relative risk is clearly higher than the effect of each risk factor alone, and exceeds the sum of the relative risks

Before accepting these estimates at face value, we have to acknowledge potential strengths and weaknesses in our design The original LETS study was not designed for the aim of this investigation, the association with minor events, however, was spontaneously noticed by the physician or investigator One third of the patients had a minor event in the weeks preceding their DVT, which is a remarkable amount This confirms the overall impression of physicians that patients often volunteer a history of minor events To study how high the frequency really is, we used the patients as their own controls, and asked them about similar minor events during an arbitrary 2 week period at the occasion of a four year follow-up investigation Since it is possible that the original spontaneous recording by physicians was elicited by some in-depth probing of the patients, we also probed rather in-depth during the follow-up patients could indicate on a questionnaire whether any of the small events had been happening recently, and they were subsequently phoned to ask the details and time window of these small events. Of course, our study is possibly hampered by the increased age and consequent changes in life habits of the patients. We did not obtain follow up on all patients, although we do think it unlikely that participation in the follow-up would be associated with the experience of a minor event Nevertheless, a bias could also be introduced in the patient group due to their familiarity with the possible risk of minor events

A number of studies with a few cases tends to support the hypothesis that minor events play a significant role in DVT We found at least twenty reports in the literature that studied the relation of thromboembolism and minor events, published between 1940 and 1998 (9-29) Most papers were descriptions of cases or case series and concerned pulmonary embolism, some with detectable DVT, mainly associated with air travel During air travel cabin related risk factors leading to hypercoagulability and hypoxia are postulated to increase the risk to develop DVT due to stasis Only few papers also described the association with other traffic (car, train, ship), immobilisation in theatre/cinema, or due to effort, strain or cramped conditions in shelters (among others 9 21, 24 27) There were few relevant larger studies One retrospective case series identified 44 patients with DVT related to air flight (from a larger retrospective series of 254 persons), of which a minority without known risk factors, but also some with injury to the lower extremity prior to travel (20) A recent formal case-control study with 160 cases and the same number of controls, investigating all modes of travel and going back several weeks in the history of the patient, found that 24 5% of patients and 7 5% of controls had a history of travel of more than five hours, leading to a fourfold increase in risk (4)

In our study the joint effect of factor V Leiden and minor events was shown to be high, at a 17 fold increase in risk of the combination This means that additional cases of DVT occur due to the synergy of minor events and factor V Leiden, which would otherwise not have occurred by either risk factor alone One should also bear in mind that several risk factors might enhance each other, e g factor V Leiden, minor events and oral contraceptive use In a recent study in patients taking oral contraceptives who developed deep-vein thrombosis or pulmonary embolism, the factor V Leiden and acquired risk factors (both minor and major events) were both found to be multiplicative risk factors over and beyond oral contraceptive use (30) Unfortunately, the relative contribution of minor and major events could not be estimated from that study These results are important, since a recent epidemic of pulmonary embolism deaths with third generation contraceptives in New Zealand concerned a number of women who had experienced minor events during use of these contraceptives (31) Rather than blaming the minor events, it becomes increasingly clear from our study and several others that the concomitant use of more thrombogenic contraceptives leads to the heightened risk (32, 33)

In conclusion, our study confirms the clinical notion that minor events are likely to play a role in the etiology of DVT, especially in the presence of hereditory thrombogenic risk factors

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