Thrombosis

Interactions between thrombophilic genetic mutations and clinical bleeding in patients on chronic oral anticoagulant treatment

We studied the prevalence of genetic thrombophilic mutations in patients on chronic oral anticoagulant treatment (OAT) who had bleeding complications. In a case-control study we found ten (12.8%) carriers of factor V Leiden and two (2.5%) carriers of the PT20210A mutation among 78 patients with a history of moderate-severe bleeding while on OAT, and seven (4.4%) and four (2.5%), respectively, among 156 matched patients with no bleeding while on OAT (odds ratio 3.1±1.6, p=0.026). In patients on chronic OAT, FV Leiden is a risk factor for moderate-severe bleeding.

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Factor V Leiden and PT20210A mutations are the most common genetic thrombophilic alterations in Caucasians[1,2] and given their high prevalence it has been suggested that they could confer an evolutive advantage, reducing bleeding. Bleeding is the most frequent complication in patients on oral anticoagulant drugs.[3] We carried out a case-control study to ascertain whether a relationship exists between the presence of genetic thrombophilic mutations and the occurrence of bleeding in a population of patients under stable, chronic oral anticoagulant treatment.

Seventy-eight subjects attending our Anticoagulation Clinic with a history of single or recurrent bleeding events were matched 1:2 with patients followed during the same period but without any hemorrhagic complications while on oral anticoagulation. Bleeds were considered severe/moderate when they required hospitalization and/or blood trasfusion and minor when they required only an outpatient evaluation, and were epistaxes requiring nasal packing (39.7%), macrohematuria (33.3%), gastrointestinal bleeding (11.5%), intracranial hemorrhage (7.7%), muscular hematomas (5.1%), hemarthrosis (2.6%) (Table1).

A follow-up analysis at two years was performed to record death, hemorrhagic complications and hospital admissions. Between October 2000 and January 2001, a predefined questionnaire, specifically concerning hemorrhagic complications, was administered by doctors working at our Anticoagulant Clinic to each patient. Moreover, when ever possible, data were extracted from hospital records, death and/or post-mortem certificates.

The quality of anticoagulant control was assessed, between January 2001 and October 2002, in a subgroup of randomly selected cases and controls, by evaluating the percentage of International Normalized Ratio (INR) values within therapeutic range, weekly warfarin dose, average INR value and percentage of INR > 5, as extracted from our database by the PARMA software package.[4]

Factor V and prothrombin exonic regions were assessed by polymerase chain reaction as described by according to Bertina *et al*.[4]

Informed consent was obtained from all the patients. The study was approved by our Institutional review board. Assuming a factor V Leiden prevalence in the general population of 5% and considering an absolute difference of 10% (from 5 to 15%) as being worth detecting the sample size needed to be 78 patients in each arm, with an α error of 0.05 and a statistical power of 0.9. Two by two contingency chi-squares were used to compare allele frequencies between groups with the STATA statistical software, release 8.0 (Stata Corp., College Station, TX, USA). We found ten factor V Leiden carriers (all heterozygotes) among the cases (12.8%) as compared with seven among the controls (4.4%) (odds ratio 3.1±1.6, 95% CI 1.1-8.6; p<0.03 (Table 1). The prevalence of the PT20210A mutation did not differ between the two groups (2.6% vs 2.6%). A history of bleeding before the start of oral anticoagulant treatment was more frequent in cases than in controls (OR 3.3±1.4, CI 1.4-7.8, p=0.007).

At follow up, higher rates of moderate-severe as well as minor bleeds were reported in cases than in controls. Mortality was higher in cases: 7.8 per 100 patients-years vs 3.2 per 100 patients-years (OR 2.7±1.2 CI 1.1-6.5; p<0.003). During the follow-up, the quality of anticoagulation control was similar in the 57 cases and the 125 controls (Table 2).

In a population of patients receiving stabilized chronic oral anticoagulant treatment we found a higher prevalence of the factor V Leiden mutation in patients who had bleeding complications than in patients who did not have hemorrhages. Follow-up analysis of our case series supports our initial observation and suggests an increase of bleeding (Table 2).

This is the first report that suggests a prohemorrhagic role for factor V Leiden, otherwise known as a thrombophilic factor. While this is unexpected, some previous observations appear to be compatible with our finding. A history of venous thromboembolism before oral anticoagulant therapy has been described as a bleeding risk factor in patients with a mechanical heart valve prosthesis prescribed prophylactic oral anticoagulants;[5] a high prevalence of the factor V Leiden mutation was found in preterm infants with intraventricular hemorrhage,[6-8] a condition associated with reductions of protein C and protein S similar to those in patients receiving oral anticoagulants: the factor V Leiden mutation might increase the risk of bleeding when a simultaneous reduction of protein C and/or protein S is present. Another possibility could be a possible linkage disequilibrium of the factor V Leiden mutation with unknown allelic variants that can modulate the bleeding tendency while on oral anticoagulants.[9]

The limitations of this study are (i) the relatively small

Table 1. Patients' characteristics.

	Cases (78)	*Controls (156)*	*OR*	*CIs*	*p*	*FVL +/- (17)*	*FVL -/- (217)*	*OR*	*CIs*	*p*
Age	70±10	68±10			ns	67±12	69±11			ns
Males/females	38/40	76/80				7/10	107/110			ns
Warfarin/acenocoumarol	73/5	146/10				17/10	202/15			
INR therapeutic range (average)	3.2	3.2			ns	3.1	3.2			ns
Duration of treatment (mo.)	103±76	100±70			ns	106±66	93±55			ns
Type of bleeding*	–	–								
epistaxis	31 (39.7%)	0				5 (29.4%)	26 (12%)	3.1±1.7	1-9.4	0.05
hematuria	26 (33.3%)	0				3 (17.6%)	23 (10.6%)	1.7±0.6	0.2-3.3	ns
gastrointestinal	9 (11.5%)	0				1 (5.9%)	8 (3.7%)	1.6±1.8	0.2-13.9	ns
intracranial	6 (7.7%)	0				1 (5.9%)	5 (2.3%)	2.6±3	0.3-24.1	ns
hematoma	4 (5.1%)	0				0 (0%)	4 (1.8%)			
hemarthrosis	2 (2.6%)	0				0 (0%)	2 (0.9%)			
≥ events	9 (11.5%)	0				0 (0%)	0 (0%)			
Factor V Leiden +/-	10/78 (12.8%)	7/156 (4.4%)		3.1±1.6	1.1-8.6	0.026				
PT2010A +/-	2/78 (2.6%)	4/156 (2.6%)	1±0.9	0.2-5.6	ns					
Bleeding history before OAT	14/76 (18.4%)	10/155 (6.4%)	3.3±1.4	1.4-7.8	0.007	3/17 (17.6%)	21/213 (9.9%)	2±1.3	0.5-7.4	ns
VTE history before OAT	9/76 (11.8%)	18/155 (11.6%)	1±0.4	0.4-2.4	ns	4/17 (23.5%)	23/214 (10.8%)	2.6±1.6	0.8-8.5	ns
Treatment indications										
PMV	42/78 (53.8%)	88/156 (56.4%)	0.9±0.2	0.5-1.6	ns	8/17 (47%)	122/217 (56.2%)	0.7±0.3	0.3-1.9	ns
AF	27/78 (34.6%)	54/156 (34.6%)	1±0.3	0.6-1.7	ns	5/17 (29.4%)	76/217 (35%)	0.8±0.4	0.3-2.3	ns
VTE	3/78 (3.8%)	5/156 (3.2%)	1.2±0.9	0.3-5.2	ns	3/17 (17.6%)	5/217 (2.3%)	9.1±7.1	2-42	0.005
Others	6/78 (7.7%)	9/156 (5.8%)	1.4±0.7	0.5-4	ns	1/17 (5.9%)	14/217 (6.6%)	0.9±1	0.1-7.3	ns

**A known risk factor at time of bleeding (urinary infection, bowel polyposis, gastric ulcer, trauma, hypertensive crisis or concomitant use of drugs potentially increasing the hemorrhagic risk) was an exclusion criterion; VTE: venous thromboembolism; OAT: oral anticoagulant treatment; PMV: prosthetic mechanical valve; AF: atrial fibrillation.*

Table 2. Follow-up analysis at two years: events in cases and controls.

	Cases	*% Patients/years*	*Controls*	*% Patients/years*	*OR*	*95%CI*	*p*
N. of patients	77		156				
Total follow up (pt/yrs)	154		312				
Bleeds							
yes/no	33/68 (48.5)	24.1	26/149 (17.4%)	17.4	4.5±1.4	2.4-8.4	0.0001
total	53/68 (77.9)	39	36/149 (24.2%)	24.1	11.1±3.9	5.6-22	0.0001
fatal*	3/77 (3.9)	1.9	3/156 (1.9%)	0.96	2.1±1.7	0.41-10.5	ns
moderarate/severe	11/68 (16.2)	8.1	9/149 (6%)	3	3±1.4	1.2-7.6	0.021
minor	39/68 (57.3)	29	24/149 (16.1%)	8	7±2.3	3.7-13.4	0.0001
secondary	10/68 (14.7%)	7.3	10/149 (0.7%)	3.3	2.2±1	0.9-5.5	ns
Bleeding history before OAT	14/76(18.4%)	9.2	10/155 (6.4%)	3.2	3.3±1.4	1.4-7.8	0.007
death (n.)							
total	12/77 (15.6%)	7.8	10/156 (6.4%)	3.2	2.7±1.2	1.1-6.5	0.003
thrombotic	3/77 (3.9%)	1.9	2/156 (1.3%)	0.6	3.1±2.9	0.5-19.1	ns
heart failure	4/77 (5.2%)	2.6	1/156 (0.6%)	0.3	1.6±0.8	0.6-4.3	ns
sudden death	0/77 (0%)	0	3/156 (1.9%)	1	1±1.2	0.1-11.1	ns
cancer	1/77 (1.3%)	0.6	1/156 (0.6%)	0.3	2.1±2.9	0.1-33	ns
unknown	1/77 (1.3%)	0.6	0/156 (0%)	0	2±2.9	0.1-33.3	ns
Hospital admission							
yes/no	34/68 (50%)	25	50/139 (36%)	18	1.8±0.5	1-3.1	0.05
total	58/68 (85.2%)	8.5	66/139 (47.5%)	24	6.4±2.4	3-13.6	0.0001
hemorrhage	9/68 (13.2%)	6.7	5/139 (3.6%)	1.8	4.1±2.4	1.3-12.7	0.01
thrombosis	5/68 (7.3%)	3.7	4/139 (2.9%)	1.4	2.7±1.8	0.7-10.3	ns
surgical dept.	21/68 (31%)	15.4	10/139 (7.2%)	3.6	4.8±2	2.1-11	<0.0001
internal dept.	22/68 (32.3%)	16.2	46/139 (33%)	16.5	1±0.3	0.5-1.8	ns
unknown	1/68 (1.5%)	0.7	1/139 (0.7%)	0.35	2.1±2.9	0.1-33.4	ns
Anticoagulant control							
INR average value	2.9±1		3.1±1				ns
weekly warfarin dose	29.8±14.5		30±14				ns
% of visits above range	15.2%		14.2%		1.08±1.30	0.85-1.37	ns

**two intracranial and one gastrointestinal bleeds were fatal in cases while one intracranial hemorrhage, one episode of macrohematuria and one multidistrict hemorrhage were fatal in controls.*

sample size, although based on a sample size that appeared to be sufficiently powered to supply the conclusion; (ii) the lack of an INR temporally related to the bleeding complications, although the overall quality of anticoagulation control in the two population was assessed during follow-up and found to be similar in both groups. Further studies, with a larger sample size and with a prospective design are required to confirm our results and to reveal the underlying mechanisms that could clarify a possible Janus-faced role of the factor V Leiden.[10]

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