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Congenital factor XI and factor VII deficiencies assure an apparent opposite protection against arterial or venous thrombosis: An intriguing observation[†]

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Objective: To investigate the prevalence and type of thrombotic events reported in patients with congenital factor XI (FXI) or factor VII (FVII) deficiency.

Patients and methods: Data on all patients with congenital FXI or FVII deficiency and a thrombotic event were gathered by means of a time unlimited PubMed search carried out in June 2014 and in February 2015. Appropriate keywords including the medical subject headings were used in both instances. Side tables were also consulted and cross-checking of the references was carried out to avoid omissions. The thrombosis event had to be proven by objective methods.

Results: Forty-three patients with FXI deficiency had arterial thrombosis and only eight had venous thrombosis. On the contrary, only five patients with FVII deficiency had arterial thrombosis whereas 31 patients had venous thrombosis. The arterial/venous ratios were 5.37 and 0.17 for FXI or FVII, respectively.

Conclusions: Arterial thrombosis is frequent in FXI deficiency whereas venous thrombosis is rare. The reverse is true for FVII deficiency. The significance of these findings is discussed especially in view of the recent use of synthetic anti-FXI compounds in the prophylaxis of post-orthopedic surgery of venous thrombosis complications.

Keywords: Factor VII, Venous thrombosis, FXI, Arterial thrombosis

The occurrence of a thrombotic complication in patients with congenital bleeding disorders represents an exceptional event. However, recent studies have shown that both arterial and venous thromboses do sometimes occur in these patients and that the event is probably not as rare as originally thought.^{1,2} These observations have stimulated research in the pathogenesis of atherothrombosis and venous thrombosis.³

Several papers have dealt with the subject and some interesting observations have become evident. The first one concerns the fact that not all congenital bleeding conditions supply the same protection from thrombosis.⁴⁻⁸ Furthermore it has been demonstrated that no thrombotic event has ever been described in congenital FX or FII deficiency.⁹ Finally, it was shown that some defects seem more protective against either arterial or venous (A/V) thrombosis.^{4,6,10}

The purpose of the present study is to compare the occurrence of arterial and venous thromboses in congenital factor XI (FXI) or factor VII (FVII) deficiency.

Patients and methods

All reported case of arterial and venous thromboses occurring in congenital FXI or FVII deficiency has been collected by (1) selection of references from personal files and papers on thrombosis in congenital bleeding disorders and (2) by a time unlimited PubMed search carried out on June 2014 and February 2015.

In the PubMed search, pertinent keywords were used. Together with the medical subject headings. Furthermore the side tables were also examined.

The references listed at the end of each new paper were checked by two of us to avoid omissions. Inclusion criteria were: a FXI or a FVII level lower than 20% of normal and an established hereditary pattern. The level of FXI or FVII antigen was also recorded but was not considered a *sine qua non* condition for inclusion.

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Cases with a FXI or FVII level greater than 20% of normal were excluded. The same occurred for sporadic cases without a proven hereditary pattern.

Associated risk factors were recorded as follows: (i) hypertension, obesity, hypercholesterolemia, smoking, diabetes, and old age (>70 years) for arterial thrombosis and (ii) obesity, oral contraceptives, congenital thrombophilia, immobilization, trauma, pregnancy, surgery, and old age (>70 years) for venous thrombosis.

The thrombotic or occlusive event had to be proven by objective methods.

These were: EKG, troponin increase, echocardiography, coronary angiography, brain CAT or MRI, and peripheral artery arteriography for arterial diseases; echography, venography, pulmonary perfusion/ventilatory scintiscan, CAT, and MRI for venous thrombosis.

Results

Forty-three patients with FXI deficiency were recorded as having had arterial occlusions. Thirty-seven of those patients had a myocardial infarction (MI) or other acute coronary syndromes, five patients had an ischemic stroke, and one had a DIC considered as peripheral artery thrombosis.^{2,4,5,10-17} On the contrary, only five patients presented a venous thrombosis.^{2,6,16} The A/V thrombosis ratio was 5.37 (Table 1). In the case of FVII deficiency, five patients had arterial thrombosis including one case of DIC, again considered as peripheral artery disease^{2,18} whereas 30 patients had venous thrombosis.^{2,19,20} Twenty-six of these had deep vein thrombosis (DVT) with or without pulmonary embolism (PE); there were two cases of superficial venous thrombosis, one case of cerebral sinuses thrombosis and one case of splanchnic vein thrombosis.

The A/V thrombosis ratio was in this case equal to 0.17 (Table 1). The difference between the two ratios was statistically significant ($P < 0.001$). Risk factors

as listed above were present in 37 of the 43 patients with arterial thrombosis and in 30 of the 35 patients with venous thrombosis.

Discussion

FXI is the intrinsic system factor that, once activated by FXII, can activate FIX, FVIII, and finally FX.

On the contrary FVII, once complexed with tissue factor, activates directly FX but there is also an indirect activation of the same factor through the activation of FIX. The end result is the activation of FX which can then convert prothrombin into thrombin in the presence of FV, phospholipids, and Ca^{++} . A defective formation of FX results in a hypocoagulable state. Since venous thrombosis is commonly maintained to be dependent of the coagulation system it would seem that venous thrombosis should result in equal proportion, regardless of the defect causing the hypocoagulability. The studies of thrombotic events occurring in congenital bleeding disorders have demonstrated that this is not the case.

There are considerable differences in the type of thrombotic events that might occur in congenital bleeding disorders. The comparison made in the present paper between FXI and FVII is the most remarkable one. Discrepancies had been observed even between the hemophilias and FVII deficiency.¹⁰ Low FXI levels seem to protect from venous thrombosis.⁶ However such low levels are not protective from atherothrombosis, safe for ischemic stroke.^{4,5} On the contrary low FVII levels do not protect from venous thrombosis but they seem to protect from arterial thrombosis.¹⁰ Quite a puzzle. In addition, high levels of FXI have been demonstrated to be a risk factor for venous thrombosis.²¹ As far as the purported protection of FXI deficiency from ischemic strokes,⁵ it has to be noted that the administration of FXI concentrates to these patients seems to eliminate such protective effect. A few fatal cases of ischemic stroke have in fact been observed after the use of these concentrates.¹⁶

Table 1 Comparison of prevalence of arterial/venous thrombosis in FXI or FVII deficiency. MI includes other acute coronary syndromes

Defect	Arterial thrombosis			Venous thrombosis					Ratio A/V	Comments
	MI	Ischemic stroke	Peripheral arteries occlusions	VTE	SVT	CST splanchnic	Total arterial	Total venous		
FXI deficiency	37	5	1	7	—	1	43	8	5,37	Approximate prevalence in the general population 1:1 000 000
FVII deficiency	1	3	1	26	1	2 (1 + 1)	5	30	0,17	Approximate prevalence 1:500 000

MI, myocardial infarction; VTE, venous thromboembolism (DVT with or without PE); SVT, superficial vein thrombosis; CST, cerebral sinuses thrombosis; A/V, arterial/venous.

Figures of arterial and venous thromboses in patients with FXI or FVII deficiency have been obtained from Refs. 1,2,4-6,10-20.

The difference in the reported cases of A/V thrombosis is so huge that cannot be modified by the high prevalence of FVII deficiency as reported to FXI deficiency in the general population (namely 1:500 000 for the former vs. 1:100 000 for the latter). This interpretation is confirmed by the large difference seen in the A/V thrombosis ratio.²⁰

Furthermore, since the incidence of possible risk factor is approximately the same, it indicates that the hypocoagulability induced by the deficiency of these two factors is different. It has a different impact on the clotting of blood.

These results are also against the theory which tend to support a common pathogenetic role for arterial and venous thromboses.

The most likely explanation for the discrepancy noted probably rests in the greater role played by blood coagulation in the pathogenesis of venous thrombosis as compared to that of arterial thrombosis. The latter depends mainly on platelets activation, dyslipidemia, and endothelial damage.²¹ These factors seem capable of overcoming the protection given by the FXI defect but not that of FVII deficiency.

A limitation of the present survey relates to the possible variability in the approach used by the different authors in the diagnosis and management of the thrombotic events present in their patients.

Furthermore, another potential limitation is the fact that FVII deficiency does not show any ethnic prevalence whereas FXI deficiency is frequent among the Jewish population.^{5,6,16}

The recent demonstration that a FXI antisense oligonucleotide has a non-inferiority protective effect on venous thrombosis after total knee arthroplasty in comparison to enoxaparin is in agreement with the conclusion of this study.²²

It remains to be explained why FXI deficiency is frequently associated with MI and other acute coronary syndromes while it is a rare cause of ischemic strokes or peripheral artery thrombosis. The present day re-evaluation of the role played by the intrinsic system on arterial and venous thromboses will certainly contribute to our understanding of the intricacies of blood clotting.^{23,24}

The observation in mice that FXI may activate FX and FV independently of FIX adds further support to the interest in the revival of studies on the contact phase of blood coagulation.^{25,26} Finally this is also in agreement with recent studies concerning prekallikrein deficiency and hypertension-related arterial diseases.²⁶⁻²⁸

Disclaimer statements

Contributors All authors have contributed equally.

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