EXCEPTIONAL CASE REPORT

blood advances

Anticoagulant therapy in patients with congenital FXI deficiency

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Key Points

- Bleeding risk of FXI deficiency on anticoagulation is unknown. We report 15 of 269 FXI-deficient subjects receiving VKA and/or DOACs.
- No major bleeding was observed for >1000 months of anticoagulation. Drug dose, monitoring and management were unaffected by FXI deficiency.

The bleeding phenotype of factor XI (FXI) deficiency is unpredictable. Bleeding is usually mild and mostly occurs after injury. Although FXI deficiency renders antithrombotic protection, some patients might eventually develop thrombosis or atrial fibrillation, requiring anticoagulant therapy. There is almost no evidence on the bleeding risk in this scenario. Our retrospective study of 269 white FXI-deficient subjects (1995-2021) identified 15 cases requiring anticoagulation. They harbored 8 different *F11* variants, mainly in heterozygosis (1 case was homozygote), and had mild to moderate deficiency (FXI:C: 20% to 70%). Two subjects (13.3%) had bleeding history before anticoagulation. Atrial fibrillation was the main indication (12/15; 80%). Fourteen patients started therapy with vitamin K antagonists (VKA), but 4 subjects were on direct oral anticoagulants (DOACs) at the end of follow-up. Over >1000 months of anticoagulation, 2 mild bleeding episodes in 2 patients (13.3%, 95% confidence interval: 3.7% to 37.9%) were recorded. No major/fatal events were reported. "Pre-post" bleeding localization and severity did not change despite treatment. On VKA, drug dosing and management were also standard, unaltered by FXI deficiency. We provide the largest description of anticoagulant use in FXI deficiency, and the first cases receiving DOACs. Although further studies are needed, our observations suggest that moderate FXI deficiency does not interfere with anticoagulant management nor bleeding risk.

Introduction

The relevance of factor XI (FXI) deficiency has undergone significant change since its discovery in 1953 by Rosenthal et al[1] in a Jewish family in the United States. FXI deficiency was thought to be similar to hemophilia and therefore was named "hemophilia C."[1] Nevertheless, further evaluation revealed that bleeding is usually mild and more commonly occurs at sites of injury and/or highly fibrinolytic tissues.[2,3] Moreover, unlike hemophilia, the bleeding phenotype of FXI deficiency is unpredictable. Neither FXI antigen nor activity is a prognostic marker.[4-6]

On the other hand, FXI deficiency confers antithrombotic protection. This fact has been proved in animal models and human cohorts.[7-9] Preis et al[9] identified 1235 FXI-deficient subjects in Israel and demonstrated that they had lower incidence of thrombosis than nondeficient individuals. These observations had encouraged the development of FXI inhibitors (anti-FXI), which may offer the opportunity to prevent major bleeding by dissociating "pathological" from "hemostatic" coagulation.[10,11]

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Given the aforementioned considerations, it has been suggested that anticoagulant therapy might not represent such a high-risk factor for bleeding in FXI deficiency. Indeed, a review suggests that FXI-deficient patients can be safely treated with vitamin K antagonists (VKA).[12] However, no systematic study has investigated bleeding in FXI-deficient individuals on anticoagulant therapy. Besides, there is no information on the effect of FXI deficiency in VKA dosing or management, nor on the use of direct oral anticoagulants (DOACs) in this setting either.

Case description

Study cohort

This study was conducted in a cohort of 269 white subjects with congenital FXI deficiency (FXI:C<70%) from 2 Spanish centers (Yecla/Murcia: N = 238, Lugo: N = 31) collected from 1995-2021. The Yecla study cohort is described elsewhere.[13]

Methods

Molecular characterization of FXI deficiency

Plasma activated partial thromboplastin time and FXI:C were determined in an automatic coagulometer (SynthASil™ and FXI-deficient plasma; Instrumentation Laboratory). Sodium dodecyl sulfate–polyacrylamide gel electrophoresis and western blot of plasma FXI were conducted with a specific antibody (GAFXI-AP190R1; Enzyme Research Laboratories). Sequencing of the exons and flanking regions of the *F11* gene by Sanger or next-generation sequencing and analysis of structural variants by MLPA were carried out in cases displaying FXI deficiency.

Patient selection criteria

We selected patients with chart-based evidence of anticoagulation during the study period. Subjects treated exclusively with prophylactic-dose heparin or antiplatelets were excluded. All included subjects gave their informed consent, which was approved by the Ethics Committee of Hospital Morales Meseguer and performed in accordance with the Declaration of Helsinki.

Data collection and analysis

Four investigators (J.E., M.J.S., E.F.-M., and A.L.) independently extracted data from medical records using a standardized form. Such data were independently checked by 2 investigators (C.B.-P. and M.E.d.l.M.-B.). Final follow-up date was June 15, 2021. Variables regarding anticoagulants comprised indication, drug, dosing, and length of therapy. Bleeding was graded according to World Health Organization (WHO) scale. In the case of VKA, the international normalized ratio (INR) and the time in therapeutic range (TTR) were collected. Statistical analysis was performed with STATAv.16 (StataCorp-LLC).

Results and discussion

Overall, we identified 269 FXI-deficient subjects carrying 22 different mutations. Only 15 had severe deficiency (FXI:C < 20%). This cohort exhibited a mild bleeding tendency. Fifty-two cases had bleeding history (19.3%; 95% confidence interval [CI]: 15.1% to 24.5%), and a high proportion of episodes occurred at sites of injury (19/52, 36.5%; 95% CI: 24.8% to 50.1%).

Thirteen subjects (4.8%; 95% CI: 2.8% to 8.1%) developed a cardiovascular event (myocardial infarction: N = 8, stroke: N = 3; transient ischemic attack: N = 2), whereas only 1 subject (0.3%, 95% CI: 0.1% to 2.1%) had a venous thrombosis. Prior works indicate that FXI-deficient patients seem to be best protected from venous thromboembolism.[9]

Fifteen cases with FXI deficiency required anticoagulant treatment (Table 1). Seven patients (46.7%) were women. Median age of this group was 70 years (interquartile range [IQR]: 64.5 to 79 years). All subjects had mild to moderate deficiency, with a median FXI:C of 40% (IQR: 33% to 48.5%).

We identified 8 different *F11* variants in these individuals. All mutations caused quantitative FXI deficiency (cross-reacting material-negative, CRM^-) in heterozygous state, except for *p.P538L*, which caused a qualitative deficiency (CRM^+) in homozygosis. Two of 15 patients had positive bleeding history before starting anticoagulation (13.3%, 95% CI: 3.7% to 37.9%), in both cases, these were mild events secondary to injury.

The main indication for anticoagulants was atrial fibrillation (AF, 12 of 15). Fourteen patients started therapy with VKA, all with acenocoumarol, but 4 subjects were on DOAC at the end of follow-up (3 sequentially, after the VKA, and 1 as frontline). All DOACs were anti-FXa (Table 1).

Median length of anticoagulation per patient was 40.4 months (IQR: 11.4-90 months). Over 1020.2 months of cumulative therapy, only 2 bleeding episodes in 2 patients (13.3%; 95% CI: 3.7% to 37.9%) were recorded. Both events were mild (WHO grade 1). Remarkably, no major/fatal bleeding was reported. It is also important to note that 2 patients received short courses of treatment-dose heparin prior to initiating oral anticoagulants, and that 4 cases were simultaneously taking antiplatelets, all of them with no evidence of bleeding. Interestingly, the "pre-post" frequency and severity of hemorrhage did not change despite the start of anticoagulation. We mention P4, 1 of the 2 subjects who bled after anticoagulant start, because he had low FXI:C (24%) and prior hemorrhagic history. The "pre-post" characteristics of bleeding were similar in this patient.

As regards VKA, median dose of acenocoumarol was 10.75 mg/wk (IQR: 8-16 mg/wk), and median TTR was 70% (IQR: 60% to 81%). Only 2 patients had TTR < 65%; in both cases it was due to INR < 2, and this was the reason for switching to a DOAC. VKA dosing and TTR did not differ significantly from the standards and seemed to be unaltered by FXI deficiency.

Patients with congenital coagulopathies are relatively protected against thrombosis, but they can eventually develop age-related thrombotic complications or AF.[14] Albeit crucial, anticoagulation might result in exacerbated hemostatic disequilibrium toward major hemorrhage. Because there is a lack of evidence-based guidelines on this scenario, the experience of exceptional cases can be of great value.[15]

In some bleeding disorders, beyond hemophilia A/B, the evidence is practically absent. This is the case of FXI deficiency. In fact, to the best of our knowledge, there are only 2 recent reports on FXI-deficient patients treated with anticoagulants, a single case and a small series (N = 5), all with VKA.[16,17] Interestingly, in parallel with our results, the only patient from these reports who had bleeding on anticoagulation also had prior history of hemorrhage, and both "pre" and "post" episodes had similar features.[17]

Table 1. Summary of FXI-deficient patients treated with anticoagulant therapy (N = 15)

ID	Sex	Age (y)	Mutation (status)	FXI:C (%)	Bleeding history pre-AC	Indication	Drug	Dose	Therapy length (mo)	For VKA, TTR (%)	Other antithrombotics	Bleeding post-AC (WHO grade)
1	M	68	p.P538L (+/+)	23	No	AF, NSTEMI	Acenocoumarol	10.5 mg/wk	2.5	66	ASA & Clopidogrel	No
2	F	70	p.C56R (+/−)	50	No	AF, By-pass	Acenocoumarol	11 mg/wk	10.9	92	Clopidogrel	No
3	M	61	p.C56R (+/−)	66	No	AF	Rivaroxaban	20 mg qd	2.3	NA	No	No
4	M	85	p.C416Y (+/−)	24	UGB (ulcer), rectal bleeding	AF, TIA	Acenocoumarol	4.75 mg/wk	58.0	75	No	Rectal bleeding (grade 1)
5	M	80	p.C599Y (+/−)	47	No	AF	Acenocoumarol	11 mg/wk	35.7	48	No	No
							Apixaban	5 mg bd	13.6	NA	No	No
6	F	92	p. I426T	39	No	AF	Acenocoumarol	8.5 mg/wk	33.0	65	No	No
7	F	74	p.C416Y (+/−)	71	No	AF, stroke	Acenocoumarol	21 mg/wk	235.5	80	No	No
8	M	34	p.C56R (+/−)	31	No	DVT	Acenocoumarol	6 mg/wk	4.0	83	LMWH (1 wk before oral AC)	No
9	F	73	p.C56R (+/−)	25	No	AF	Acenocoumarol	5 mg/wk	11.4	19	No	No
							Edoxaban	60 mg qd	10.6	NA	No	No
10	M	69	p.C416Y (+/−)	41	No	AF	Acenocoumarol	31.5 mg/wk	124.2	61	No	No
							Edoxaban	60 mg qd	6.8	NA	No	Gingiva bleeding (grade 1)
11	F	26	Ins 1653 bp (+/−)	46	No	Univentricular surgery; TGA & PS	Acenocoumarol	14 mg/wk	31	55	ASA	No
						Post stent		26 mg/wk	200	60	ASA	No
12	F	70	p.R268C (+/−)	35	No	AF	Acenocoumarol	10 mg/wk	75.7	55	No	No
13	M	80	ND	40	Tooth extraction	AF	Acenocoumarol	16 mg/wk	90.0	100	No	No
14	F	78	p.C416Y	38	No	AF	Acenocoumarol	12 mg/wk	30.0	81	LMWH (2 mo before oral AC)	No
15	M	52	p.E135* (+/−)	59	No	NSTEMI (aPLS)	Acenocoumarol	8 mg/wk	45.0	74	No	No

AC, anticoagulation; AF, atrial fibrillation; aPLS, antiphospholipid syndrome; ASA, acetylsalicylic acid; bd, twice daily; DVT, deep venous thrombosis; F, female; LMWH, low-molecular-weight heparin; M, male; NA, not applicable; NSTEMI, non-ST segment elevation myocardial infarction; PS, pulmonary stenosis; qd, every day; TGA, transposition of great arteries; TIA, transient ischemic attack; UGB, upper gastrointestinal bleeding.

Our observations may be highly relevant to the fascinating possibilities opened by anti-FXI.[18,19] Noteworthy, only 15 subjects from our cohort (5.6%), and none of the 15 patients with severe deficiency, had thrombotic events requiring anticoagulants. Moreover, because the grade of suppression achieved by anti-FXI is compatible with moderate deficiency, and it may not substantially increase the bleeding risk over that conferred by VKA or DOAC, the addition of anti-FXI on standard anticoagulation would be beneficial when required without accentuating bleeding risk.[10,11]

In conclusion, despite the retrospective analysis and the low sample size owing to a rare disease, we report the largest descriptive study on anticoagulation in FXI deficiency, and the first cases receiving DOAC. Our clinical observations suggest, in consonance with prior reports, that moderate FXI deficiency does not seem to significantly interfere with anticoagulant management nor bleeding risk. Future works should focus on this issue, particularly to evaluate patients with severe deficiency, in whom our results cannot be extrapolated, and confirm if some variables, such as prior history of bleeding, can guide clinical decisions. Finally, our findings provide further evidence that may be connected to the fascinating possibilities opened by FXI inhibition.

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Authorship

Contribution: J.E., M.J.S., E.F.-M., E.F.-T., A.L., and M.C.-S. recruited all patients, were responsible for clinical and coagulation data, and reviewed medical charts; C.B.-P. and M.E.d.l.M.-B. independently revised extracted data; C.B.-P., M.E.d.l.M.-B., J.P., and A.M. were responsible for molecular, functional, and biochemical characterization of FXI deficiency; J.E., V.V., and J.C. designed the research plan

and coordinated the experimental work; C.B.-P., M.E.d.l.M.-B., V.V., and J.C. interpreted the results and drafted the manuscript; and V.R. contributed to the critical revision of anticoagulant data.

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References

1. Rosenthal RL, Dreskin OH, Rosenthal N. New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. *Proc Soc Exp Biol Med.* 1953;82(1):171-174.
2. Seligsohn U. Factor XI deficiency in humans. *J Thromb Haemost.* 2009;7(suppl 1):84-87.
3. Salomon O, Steinberg DM, Seligshon U. Variable bleeding manifestations characterize different types of surgery in patients with severe factor XI deficiency enabling parsimonious use of replacement therapy. *Haemophilia.* 2006;12(5):490-493.
4. Ragni MV, Sinha D, Seaman F, Lewis JH, Spero JA, Walsh PN. Comparison of bleeding tendency, factor XI coagulant activity, and factor XI antigen in 25 factor XI-deficient kindreds. *Blood.* 1985;65(3):719-724.
5. Santoro C, Di Mauro R, Baldacci E, et al. Bleeding phenotype and correlation with factor XI (FXI) activity in congenital FXI deficiency: results of a retrospective study from a single centre. *Haemophilia.* 2015;21(4):496-501.
6. Guéguen P, Galinat H, Blouch M-T, et al. Biological determinants of bleeding in patients with heterozygous factor XI deficiency. *Br J Haematol.* 2012;156(2):245-251.
7. Wang X, Smith PL, Hsu M-Y, et al. Effects of factor XI deficiency on ferric chloride-induced vena cava thrombosis in mice. *J Thromb Haemost.* 2006;4(9):1982-1988.
8. Gruber A, Hanson SR. Factor XI-dependence of surface- and tissue factor-initiated thrombus propagation in primates. *Blood.* 2003;102(3):953-955.
9. Preis M, Hirsch J, Kotler A, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood.* 2017;129(9):1210-1215.
10. Fredenburgh JC, Gross PL, Weitz JI. Emerging anticoagulant strategies. *Blood.* 2017;129(2):147-154.
11. Srivastava P, Gailani D. The rebirth of the contact pathway: a new therapeutic target. *Curr Opin Hematol.* 2020;27(5):311-319.
12. Salomon O, Seligsohn U. New observations on factor XI deficiency. *Haemophilia.* 2004;10(suppl 4):184-187.
13. Esteban J, de la Morena-Barrio ME, Salloum-Asfar S, et al. High incidence of FXI deficiency in a Spanish town caused by 11 different mutations and the first duplication of F11: results from the Yecla study. *Haemophilia.* 2017;23(6):e488-e496.
14. Philipp C. The aging patient with hemophilia: complications, comorbidities, and management issues. *Hematology (Am Soc Hematol Educ Program).* 2010;2010(1):191-196.
15. Martin K, Key NS. How I treat patients with inherited bleeding disorders who need anticoagulant therapy. *Blood.* 2016;128(2):178-184.
16. Bauduer F. Uneventful long-term anticoagulation with fluindione in a patient with severe factor XI deficiency. *Haemophilia.* 2015;21(1):e72-e73.
17. Chapin J, Klute K, Christos P, DeSancho M. The safety of chronic antithrombotic therapy in patients with factor XI deficiency. *Br J Haematol.* 2017;179(3):506-508.
18. Büller HR, Bethune C, Bhanot S, et al; FXI-ASO TKA Investigators. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med.* 2015;372(3):232-240.
19. Verhamme P, Yi BA, Segers A, et al; ANT-005 TKA Investigators. Abelacimab for prevention of venous thromboembolism. *N Engl J Med.* 2021;385(7):609-617.