Factor XI Deficiency

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Factor XI (FXI) deficiency leads to an injury-related bleeding diathesis, which is notable for the variability in the bleeding tendency and the lack of a clear relationship between bleeding and FXI coagulant activity. Bleeding in this disorder occurs especially in areas of high fibrinolytic activity. Although a rare disorder, the frequency of FXI deficiency is high in certain populations, notably persons of Ashkenazi descent and the Basque population of Southern France. In these populations, five mutations of the FXI gene have been identified and a founder effect has been confirmed for three of these. This paper reviews the role of FXI in coagulation and documents factors known to modify the bleeding tendency. Treatment of surgical bleeding in patients with FXI deficiency is reviewed with emphasis on the combined use of recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) and the antifibrinolytic agent, tranexamic acid.

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FACTOR XI (FXI) is the zymogen of a serine protease, which activates factor IX (FIX) and thus augments thrombin generation on the surface of activated platelets in the consolidation phase of coagulation.[55] Deficiency of this factor leads to an injury-related bleeding diathesis, which was first described in 1953 and has been historically termed "hemophilia C," "plasma thromboplastin antecedent deficiency," and "Rosenthal syndrome."[36,45,47] The bleeding disorder is now known as "factor XI deficiency" and is remarkable for the variability in the bleeding tendency and the lack of a clear relationship between bleeding and FXI coagulant activity (FXI:C).[10,12,50] Normal levels of FXI range from 70 to 150 U/dL (12). Heterozygotes for a mutation in the FXI gene have a partial deficiency of FXI and have levels between 20 and 70 U/dL.[10] Homozygotes or compound heterozygotes for a causative mutation have a severe deficiency of FXI and their FXI:C levels are less than 20 U/dL.[1] Bleeding is associated with surgery or trauma and spontaneous bleeding is exceedingly rare. A clear relationship between excessive bleeding and injury to areas of high intrinsic fibrinolytic activity has been noted.[1]

FXI deficiency has been reported from diverse populations at a frequency of one per million. However, the frequency of this condition is much higher in certain populations, notably persons of Ashkenazi descent, who have a heterozygote frequency of 9% and a homozygote frequency of 0.22%.[52] Four mutations (termed types I to IV) have been described in Jewish communities, of which type II and III mutations account for 98% of the mutant alleles. In fact, FXI deficiency is found in all Jewish populations, although Ashkenazi Jews have the highest incidence as a consequence of the presence of both of the common mutations.[43] Analysis of intragenic polymorphisms has confirmed a founder effect for the two common Jewish mutations and has also proven a founder effect in the Basque population of Southern France, in which a unique mutation in the FXI gene is found in approximately 1% of the population.[56] An increasing number of mutations are being reported in non-Jewish patients; these are documented at the Human Gene Mutation Database, Cardiff, UK (www.uwcm.ac.uk/uwcm/mg/hgmd0.html).

Role of FXI in Coagulation

There are a number of conundrums associated with the role of FXI in the coagulation cascade. First, the realization that activated FVII (FVIIa) and tissue factor (TF) can activate FIX and thus initiate coagulation via the intrinsic as well as the extrinsic systems, called into question the role of the contact factors.[46] Indeed, deficiencies of the contact factors, FXII, high-molecular-weight kininogen (HMWK), and prekallikrein, do not lead to a clinical bleeding phenotype. Unlike the majority of the clinically important coagulation serine proteases, FXI does not contain a GLA domain to interact with the platelet surface. The FXI protein is also unique among coagulation proteins in that it exists as a homodimer, with each individual FXI protein consisting of four tandem apple domains linked to a typical serine protease domain.[14] FXI circulates in a complex with HMWK and Zn^{2+} ions.[20]

Advances in the understanding of the biochemistry of FXI in recent years have explained some of

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these conundrums. Thrombin is the physiological activator of FXI rather than FXIIa as previously thought.[4,5] The small amounts of thrombin, which are generated in the initiation phase of coagulation, are sufficient to activate FXI, which can then activate FIX and further increase the thrombin-generating potential of the consolidation phase of coagulation. Despite the fact that FXI is known as a contact factor, activated platelets, rather than negatively charged surfaces, provide a preferential surface for the activation of FIX by FXI.[5,6] The binding of FXI to activated platelets occurs via the third apple domain of FXI and platelet glycoprotein Ib/IX/V.[2,3,24,28] Prothrombin and Ca^{2+} ions can substitute for HMWK/Zn^{2+}, explaining why deficiencies of HMWK do not lead to bleeding.[27]

The role of FXI in the coagulation cascade may be summarized as follows. Small amounts of thrombin, generated by the exposure of FVIIa/TF at the site of vessel injury during the initiation phase of coagulation, serve to activate platelets and FXI. Subsequent binding of FXI to activated platelets via apple 3 and GPIb localizes FXI to the surface on which the consolidation phase of coagulation occurs.[37] The dimeric structure of FXI may be important for the dual roles of platelet binding and substrate activation. A recent hypothesis suggests that binding to platelets occurs via the apple 3 domain of one of the FXI proteins in the dimer, which leaves the apple 3 domain of the other FXI molecule available for substrate binding.[22] Although FVIIa/TF can activate FIX, this pathway is rapidly inhibited by tissue factor pathway inhibitor (TFPI). The activity of the primary inhibitor of FXI, protease nexin II, is confined to the fluid phase and therefore platelet-bound FXI is able to freely activate FIX and thus provide a burst of thrombin localized to the site of vessel injury.[55]

Modifiers of the Bleeding Tendency in FXI Deficiency

Co-inherited Bleeding or Thrombotic Disorders

In view of the lack of correlation between bleeding and FXI levels, other hemostatic modifiers such as co-inherited bleeding or thrombotic disorders have been considered. Von Willebrand's disease (vWD) was diagnosed in 13% of the patients with FXI deficiency in a small study.[53] Bolton-Maggs et al did not find an increased incidence of type I vWD, but did find a correlation between von Willebrand factor antigen (vWF:Ag) levels and bleeding.[10] Sixty-two percent of patients with vWF:Ag less than 70 U/dL, in addition to a partial deficiency of FXI, had an increased incidence of bleeding. However, the use of a vWF level of 70 U/dL to predict bleeding tendency would lead to a 25% false-positive rate. Patients with blood group O had slightly lower levels of vWF:Ag and a slightly increased risk of bleeding symptoms, but these differences did not reach statistical significance.

Co-inherited thrombophilic traits have been reported to alleviate bleeding symptoms in patients with hemophilia. Heterozygosity for the FV Leiden mutation reduced concentrate usage and the number of bleeding episodes in patients with severe hemophilia A.[35] The influence of these traits on the clinical phenotype of FXI-deficient patients requires further study.

FXI Genotype

In a study of 52 unrelated patients with severe FXI deficiency, the mean number of injury- or surgery-related bleeding events was significantly higher in patients with the II/II genotype(1.6 ± 2.4) versus patients with a II/III (1.4 ± 1.5) or a III/III (1.0 ± 1.1) genotype ($P < .05$ for both comparisons).[1] However, when the site of surgery was considered, the majority of patients bled after surgery in an area with high intrinsic fibrinolytic activity or after dental extraction, regardless of genotype. Another study of 63 patients with homozygous and heterozygous FXI deficiency, analyzed bleeding symptoms in relation to genotype.[25] Compound heterozygotes for the II/III mutations were more likely to have a moderate rather than a mild bleeding tendency, but the number of patients in each genotype group was small. Bleeding symptoms in heterozygotes were not associated with particular genotypes in this study. No correlation between the underlying mutation in the FXI gene and the bleeding tendency has been identified in partially deficient patients.[10]

FXI Inhibitors

Inhibitors to FXI were reported very rapidly after the original description of the deficiency.[32] A study of the prevalence and the functional characteristics of FXI inhibitors in 118 severely deficient patients was undertaken recently.[48] Inhibitors were detected in seven patients, all of whom were homozygous for the type II mutation with a history of exposure to plasma-derived FXI treatment, giving a rate of inhibitor development of 33% in this subgroup. Patients with this mutation who had not been transfused did not develop inhibitors, nor did transfused patients with other mutations. The rate of transient inhibitor development was not assessed prospectively in this study.

Inhibitors are usually detected clinically as breakthrough bleeding and/or a worsening response to FXI replacement perioperatively, rather than by spontaneous bleeding. Investigation for inhibitor develop-

ment should be considered in patients with a II/II genotype who have been previously transfused and who develop an unexpected poor response to treatment or a worsening clinical phenotype.

FXI and Fibrinolysis

An association between surgery or trauma to areas of high intrinsic fibrinolytic activity and bleeding in FXI-deficient patients has been well described.[1,10] Thrombin activatable fibrinolysis inhibitor (TAFI) is an important modulator of fibrinolysis and requires the high concentrations of thrombin generated in the consolidation phase of coagulation for activation.[21,41] Activation of TAFI has been shown to be significantly FXI-dependent, leading to downregulation of fibrinolysis in the presence of normal concentrations of FXI.[15,19] The concentration of TAFI antigen in blood is variable and this variability is associated with the presence of specific polymorphisms and, in cardiovascular disease, with clinical phenotype.[17,33] The influence of TAFI antigen and activity levels on the bleeding phenotype in FXI-deficient patients has yet to be determined.

Platelet Factor XI

Tissue-specific expression of platelet FXI and its contribution to coagulation has been the subject of conflicting reports. Initial reports suggested that platelet FXI was present in an alternatively spliced form, which lacked exon V and was present despite the lack of plasma FXI.[30,31,51] However, another group found only wild-type FXI mRNA in platelets, leukocytes, and bone marrow.[39]

Treatment of FXI Deficiency

Currently available therapy for FXI deficiency consists of antifibrinolytic agents and FXI replacement.[13] As mentioned, bleeding is especially likely in areas of high fibrinolytic activity in patients with FXI deficiency and, therefore, antifibrinolytic agents have been used extensively in this condition. Tranexamic acid is the most frequently used agent and has the advantage that it can be given orally as a tablet or a 5% mouthwash as well as intravenously. Dental extraction in severely deficient patients has been managed successfully with tranexamic acid alone and with topical fibrin glue.[7,44]

FXI replacement is achieved by the use of fresh-frozen plasma (FFP) or FXI concentrate. Solvent-detergent treated FFP (SD-FFP) is preferred due to improved viral safety.[54] Treatment with SD-FFP may lead to volume overload and allergic reactions and may not result in normalization of the FXI:C activity in severely deficient patients.[18] FXI concentrate is manufactured in the United Kingdom by BioProducts Laboratory (BPL, Elstree, Herts, UK) and in France by Laboratoire Francais du Fractionnement et des Biotechnologies (LFB, Les Ulis-Courtaboeuf, France).[11,16] It is an unlicensed product, available on a named patient basis and is not freely available in many countries including the United States. A number of reports of thromboembolic side effects emerged after these concentrates were introduced.[9,23,38] Manufacturing changes were introduced to prevent the infusion of activated FXI in the concentrate and recommendations on maximum doses and exclusion of patients with pre-existing risk-factors for thrombosis were made.[13] Subsequently, a review of experience of FXI concentrate over a 5-year period in a single center using the clinical guidelines and the BPL concentrate has not revealed any case of thrombosis.[42] Therefore, it will be appreciated that while FXI replacement is often desirable to prevent surgical bleeding, FFP and FXI concentrate may be unsuitable for a significant number of patients. In addition, both are plasma derived and carry a potential risk of transfusion-transmitted infection.

Recombinant Factor VIIa in the Treatment of FXI Deficiency

An alternative to the treatment options outlined above is required for FXI-deficient patients. Ideally, such a treatment should be recombinant and capable of replacing the role of FXI in coagulation. Recombinant factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) fulfills these requirements, in particular because it generates a burst of thrombin on the surface of the activated platelet.[29,40] The use of rFVIIa in factor XI deficiency was first reported in 1990 when rFVIIa was used to prevent surgical bleeding in a patient with an inhibitor to FXI undergoing orchidectomy.[26] Since then, a small number of case reports in patients with and without inhibitors have confirmed that rFVIIa is effective in preventing surgical hemorrhage.[8,34]

A pilot study was initiated to further assess the efficacy and safety of rFVIIa in FXI deficiency. Consecutive FXI-deficient patients who presented for elective surgery and who had an indication for FXI replacement were recruited to the study. The treatment protocol is outlined in Table 1. The primary trial endpoints were hemostatic efficacy, as evaluated by clinical examination and the use of additional hemostatic agents or blood products, and safety, as evaluated by reporting of adverse events.

Patient characteristics are given in Table 2. Fifteen procedures in 14 patients (median age, 42.5 years; range, 20 to 77 years) were successfully performed without any evidence of bleeding and without the need for additional hemostatic agents. One patient

Table 1. Treatment Protocol

Procedure	Day	Dose rFVIIa*	Dose Interval	No. of Doses
Minor/dental	1	90 μg/kg	4-hourly	2
Major	1	90 μg/kg	2-hourly	13
	2	90 μg/kg	4-hourly	6

NOTE. Tranexamic acid was given (15 mg/kg orally 6-hourly) for 7 days postoperatively in all cases.

* The first dose of rFVIIa is given immediately preoperatively in all cases.

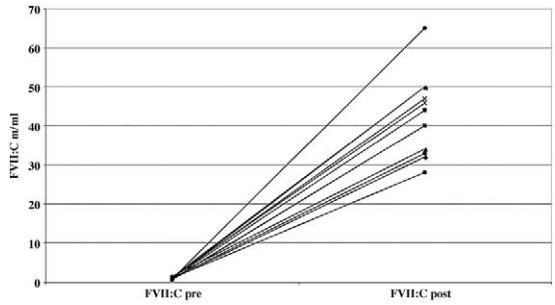

Figure 1. FVII:C levels pre- and post-rFVIIa first dose for all 15 procedures. All pre-FVII:C levels were within the normal range (0.5 to 1.5 U/mL). Note that some patients had identical post rFVIIa FVII:C levels (three patients: 50 U/mL; two patients: 46 U/mL; two patients: 44 U/mL; two patients: 40 U/mL).

underwent two separate dental procedures. Laboratory investigations revealed that FVII:C increased after administration of rFVIIa but there was considerable interindividual variation (Fig 1). The thrombelastogram was evaluated pre- and post-rFVIIa in eight patients undergoing nine procedures and showed correction in the reaction (r) and clot formation (k) times in all cases.[49]

Three adverse events were documented during the study. An elderly male patient with a remote history of coronary artery disease developed clinical and radiological evidence of a cerebrovascular infarct after 48 hours of treatment with rFVIIa and died 3 days later. A female patient with a strong history of atopy developed periorbital rash and itching associated with mildly elevated liver function tests. These symptoms resolved after discontinuation of treatment and she is now being investigated for possible allergy to components of the vial bung. A third patient developed a mild local phlebitis, which resolved with conservative therapy.

This pilot study demonstrates that rFVIIa, when given with tranexamic acid, is effective in preventing bleeding after surgical procedures in patients with FXI deficiency. The use of rFVIIa avoids exposure to human plasma. rFVIIa is also effective in patients with inhibitors to FXI. However, the risk of thrombosis remains in patients with other risk factors for thromboembolic disease. In all patients, careful consideration of the risks and benefits of surgery and the options for hemostatic cover is indicated. Further study of the use of rFVIIa in patients with FXI deficiency is required to determine the optimal dose and dose schedule of rFVIIa, to clarify the role of concomitant antifibrinolytics, and to investigate the potential of treatment with rFVIIa to reduce the incidence of inhibitor development in patients who are homozygous for the type II mutation.

Table 2. Patient Demographics and Procedures

Characteristics	No. of Patients
Gender	
Male	7
Female	7
Ethnic origin	
Jewish	9
Non-Jewish	5
Severity of FXI deficiency	
Severe (<15 U/dL)	5
Partial (20-70 U/dL)	9
Positive bleeding history	11
Inhibitors to FXI	1
Procedure	
Major	5
Minor	4
Dental	6

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