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FACTOR XI DEFICIENCY AND ITS MANAGEMENT

Third Edition

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Treatment of Hemophilia Monographs
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Paula H.B. Bolton-Maggs

Summary

Factor XI (FXI) deficiency has a more variable bleeding tendency than hemophilia A or B. Individuals with severe deficiency have only a mild bleeding tendency, which is typically provoked by surgery, but the risk of bleeding is not restricted to individuals with severe deficiency. The bleeding tendency varies among individuals with similar FXI levels, and sometimes the bleeding tendency of an individual may vary. The reasons for this are not fully understood, although in cases of severe deficiency there is some correlation between phenotype and genotype.

FXI is activated by thrombin. The role of FXI in physiological processes has become clearer since this fact was discovered, and the discovery has contributed to a revised model of blood coagulation. FXI deficiency occurs in all racial groups, but is particularly common in Ashkenazy Jews. The FXI gene is 23 kilobases long. Two mutations are responsible for most FXI deficiency in the Ashkenazy population, but several other mutations have now been reported in other racial groups.

Individuals with FXI deficiency may need specific therapy for surgery, accidents, and dental extractions. Several therapies are available, which include fresh frozen plasma, FXI concentrates, fibrin glue, antifibrinolytic drugs, and possibly desmopressin. Each has advantages and risks to be considered. Factor XI concentrate may be indicated for procedures with a significant risk of bleeding, especially in younger patients with severe deficiency, but its use in older patients has been associated with thrombotic phenomena. If fresh frozen plasma is to be used, it is preferable to obtain one of the viral-inactivated products. Fibrin glue is a useful treatment which deserves further study.

Introduction

FXI deficiency, originally called hemophilia C, is distinguished from hemophilia A and B by the absence of bleeding into joints and muscles and by its occurrence in individuals of either sex. Individuals with FXI deficiency may or may not have a mild bleeding tendency, which is typically provoked by surgery. The bleeding risk is not as clearly influenced by the severity of the deficiency, as is the case in hemophilia A and B where the bleeding tendency is more clearly related to factor level. The unpredictable nature of FXI deficiency means that the clinical management of this disorder is more difficult than for hemophilia A or B.

With the discovery that coagulation factor XI (FXI:C) can be activated by thrombin, the physiological role of FXI:C in blood coagulation became clearer. This discovery led to a revised model of coagulation [1] which, together with information from molecular genetics, has contributed to renewed understanding of this disorder.

Biochemistry and the Role of Factor XI in Blood Coagulation

Traditionally FXI was one of the "contact" factors (i.e., factors not required for normal hemostasis), and its physiological role in blood coagulation was poorly understood. FXI is a two-chain serine protease, with each chain composed of 607 amino acids. Activation by factor XIIa (FXIIa) results in cleavage at a single arginine^{369} - leucine^{370} bond, producing a four-chain activation product (FXIa) with two light chains containing the active site and two heavy chains which contain binding sites for high molecular weight kininogen (HMWK) and calcium [2]. The heavy chain contains four tandem repeats (apple domains) and is 396 amino acids long. The overall sequence shows considerable homology with prekallikrein (58%) [3], especially in the light chain (81%). These two proteins compete for binding to HMWK, but have different substrates with little cross-reaction, suggesting that small differences in sequence are important for specificity of substrate binding.

Surface-bound FXIa, in turn, activates factor IX (FIX), but the importance of this *in vivo* is not clear since no defect in FIX activation can be demonstrated in individuals with FXI deficiency [4]. Although individuals with FXI deficiency have a bleeding tendency, it is mild in comparison with deficiencies of factor VIII (FVIII) and FIX. Individuals with undetectable FXII, HMWK, or prekallikrein do not exhibit any bleeding tendency.

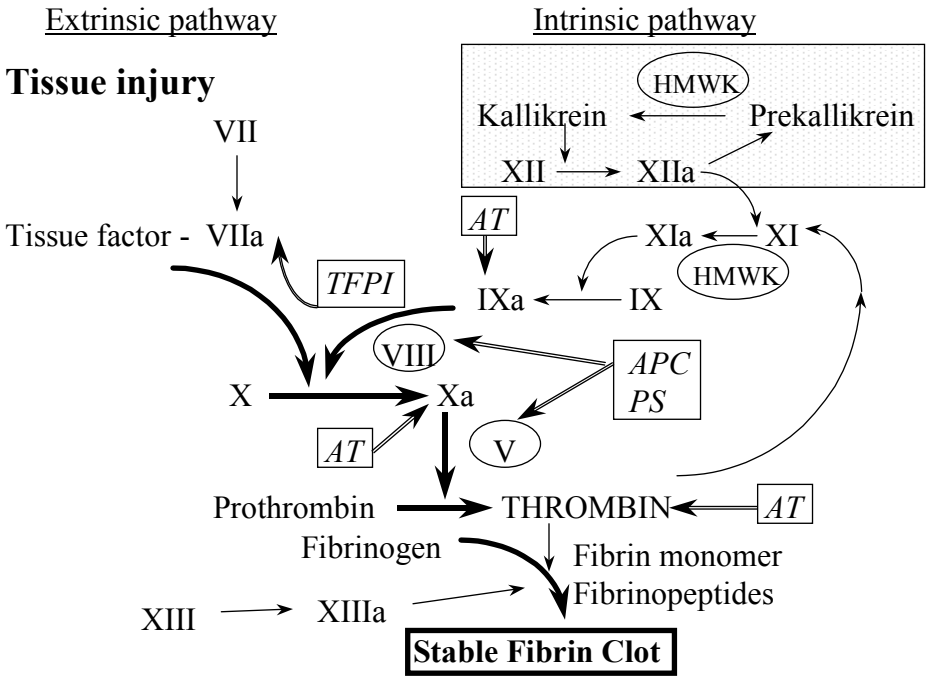
These and other findings have resulted in a revised model of coagulation shown in Figure 1. Coagulation is normally triggered *in vivo* via tissue factor (TF) and the extrinsic pathway. Small amounts of thrombin so generated activate platelets and FXI on the platelet surface via its Gp1b receptor. Back-activation of the intrinsic pathway modulates coagulation activation without involvement of the rest of the "contact" system and provides an ongoing stimulus for the coagulation pathway as the factor VIIa-TF (FVIIa-TF) is inactivated by the extrinsic pathway inhibitor [5]. FXI is also found in platelets, and is thought to originate from a megakaryocyte gene; it has been found in platelets of patients with severe plasma FXI deficiency who do not bleed after surgery [6, 7]. The role and nature of platelet FXI is not fully resolved.

FXI:C has no known role in the complement or kinin pathways, but has been shown to activate fibrinolysis [8]. Although a defect of fibrinolysis can be demonstrated in people with FXI deficiency [9], it is not clear whether this has any physiological significance. There are a number of inhibitory molecules for FXIa in plasma, including alpha 1 antitrypsin, C1 esterase inhibitor, antithrombin III, and alpha 2 antiplasmin. In the environment of the activated platelets, protease nexin II, secreted from platelet alpha granules, is important [6].

Figure 1: Revised Hypothesis of Blood Coagulation

Coagulation inhibitors □ : TFPI = tissue factor pathway inhibitor. APC= activated protein C.
PS = protein S. AT = antithrombin. Coagulation co-factors ◯ : HMWK = high molecular weight kininogen.

Coagulation is initiated at a site of vessel damage when factor VIIa is exposed to tissue factor. Factors VIII, IX, and XI are required for the production of additional factor Xa due to feedback inhibition of the factor VIIa/tissue factor complex by TFPI. The "contact pathway" is enclosed within a box – the factors therein are not required for normal hemostasis; the idea of "extrinsic" and "intrinsic" pathways is no longer an adequate concept. The assembly of coagulation proteins occurs on phospholipid surfaces, particularly platelets.



Clinical Picture and Inheritance

FXI deficiency is distinguished clinically from hemophilia A and B by the absence of spontaneous bleeding into joints and muscles and by its occurrence in individuals of either sex. It was first identified in a Jewish family. Two sisters bled after dental extraction and tonsillectomy, and their maternal uncle bled after dental extraction but had had a normal infantile circumcision [10, 11]. Four other affected individuals were identified among the 13 family members from four generations, with considerable variation in the degree of laboratory abnormality and bleeding tendency.

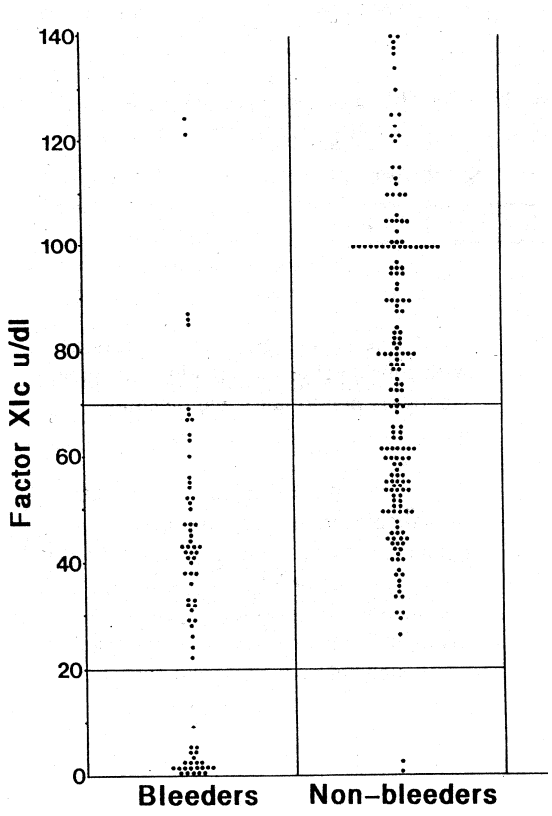
Following standardization of the partial thromboplastin time (by the addition of kaolin to provide optimal surface activation) a one-stage FXI:C assay came into routine use. This enabled physicians to distinguish between severe (homozygous or compound heterozygous) and partial (heterozygous) FXI deficiency [12, 13]. Inheritance of the deficiency was disputed. Some groups reported it to be autosomal dominant because symptoms occurred in parents and offspring [11, 14, 15], but it was more widely reported as autosomal recessive because individuals with partial deficiency were thought not to have a bleeding tendency.

An early study of eight patients and their families showed severe deficiency (FXI:C below 20 U/dL) to be associated with postoperative bleeding. Patients with partial deficiency who had levels of 30 to 60 U/dL had "no serious bleeding after surgery or dental extraction" [12]. The study included data from 36 patients who underwent 94 procedures, 85 with no bleeding. In nine procedures "slight" bleeding occurred, which included oozing that started several days after dental extractions and was controlled by packing, and one episode of vaginal bleeding that required packing three weeks after vaginal hysterectomy.

A second study of 10 Jewish family members from Israel confirmed the pattern of inheritance. However, several patients with partial deficiency had a history of bleeding (most commonly bleeding after dental extractions or tonsillectomy, which was sometimes severe). Researchers noted the lack of absolute relationship between bleeding history and FXI [13]. Further studies have confirmed that between 20 and 50% of individuals with partial deficiency bleed excessively [16-21]. Figure 2 shows data from studies in the U.K.

Description of the inheritance of FXI deficiency as "recessive" is therefore misleading because it implies that individuals with partial deficiency do not have symptoms. The differing views on inheritance in the literature may reflect differences in the definition of what constitutes "abnormal" FXI:C levels, and the presence or absence of additional imbalances in coagulation in particular individuals and their relatives (see discussion below).

Figure 2: The Relationship Between FXI:C Level and Bleeding Tendency



Pooled data from two U.K. studies [18, 19] involving 249 individuals from 54 families transmitting factor XI deficiency. Of 128 individuals with partial factor XI deficiency, 45 (35%) are bleeders. The upper horizontal line defines the lower limit of the normal range, and the lower line the cut-off between severe and partial factor XI deficiency. (Reprinted with permission from Bolton-Maggs, 1996).

People with partial deficiency have FXI:C levels between 15-20 U/dL and the lower limit of the normal range, which is variably defined. Many hospitals quote 50 U/dL, but when the normal range is derived by taking two standard deviations either side of the mean of a group of normals, values range between 63 U/dL [12] and 80 U/dL [13] [1]. Caution is needed because individuals have been reported with a bleeding tendency with FXI:C levels between 50 and 70 U/dL [18].

Individuals with severe FXI deficiency (FXI:C below 15 to 20 U/dL) are usually at risk of excessive bleeding after surgery and injury. However, paradoxically, some people with severe deficiency do not have a bleeding tendency [22-25]. The bleeding risk will depend upon the type of surgery and is increased in areas of high fibrinolysis (such as the mouth and nose). In contrast to severe hemophilia A and B, spontaneous bleeding is not usually a feature, but can occur. Cases have been reported of individuals who suffered a massive hemothorax [15], a cerebral hemorrhage [26], a subarachnoid hemorrhage [27], and a spinal epidural hematoma with Brown-Sequard syndrome [28]. Spontaneous hemarthroses are rare but have been reported, even in individuals with partial deficiency [29]. Hematuria [13] and menorrhagia are associated with FXI deficiency [12-14, 30-33]. Other studies have excluded heavy menstrual bleeding as a relevant symptom of a bleeding disorder [16, 17] because of the difficulty of objectively assessing it [34]. More recent studies have confirmed that women with FXI deficiency are prone to menorrhagia [19, 35].

Reasons for the unpredictable bleeding tendency in FXI deficiency are not fully understood. Possible factors include variant FXI molecules, additional clotting factor disorders, platelet defects and platelet FXI, and the role of fibrinolysis at sites of injury.

Variant FXI molecules

Researchers have conducted immunological assays to find evidence for abnormal FXI molecules [9, 16, 19, 36], but a discrepancy between FXI:C compared with antigen (i.e., cross-reacting material positive, CRM+) is very rare and has only been found in a few individuals, including members of three German [16, 37], one Japanese [38], and two French families [39].

Additional clotting factor disorders

Several cases have been reported of individuals who have hemophilia A or von Willebrand disease (VWD), as well as FXI deficiency [reviewed in 19]. Recent Israeli studies show a more consistent association. Most of the bleeding in partial FXI deficiency could be explained by the presence of VWD [40]. Conversely, in another study, the bleeding tendency in individuals with VWD was predicted by the FXI:C level and von Willebrand factor (VWF) antigen level using logistic regression analysis [20]. Using similar methods in patients with FXI deficiency, bleeding was predicted with a specificity of 85%. The proportional odds logistic model was fitted to bleeding grades (established using a detailed questionnaire and extensive patient interview) with the following variables: sex, age, age at diagnosis, bleeding history, FXI:C level, FXI genotype, FVIII:C level, VWF antigen and activity, and blood group. Not surprisingly, severe FXI deficiency was a strong predictor of bleeding. FVIII:C levels were correlated with FXI:C levels, but neither this nor VWF level predicted bleeding [41].

A study conducted in the U.K., where the genetic basis for both FXI deficiency and VWD may be different, did not find the associations to be so clear-cut. It demonstrated a statistically significant difference in VWF levels (but still within the normal range) between patients with a partial deficiency who had a history of bleeding compared with non-bleeders with similar FXI:C levels [19].

A comprehensive survey of multiple coagulation factor deficiencies includes four families with combined FVIII, FIX and FXI deficiencies and two families with combined FIX and FXI deficiencies, described as two previously uncharacterized familial multiple factor deficiency syndromes (FMFD V and VI)—i.e., each was believed to be caused by a single genetic disorder [42].

Platelet defects and platelet factor XI

The role of FXI in platelets needs to be clarified (see page 2). Platelet FXI has been detected in

[1] Analysis of 103 blood donors gives a mean of 99 U/dL and normal range of 60 to 139 U/dL (+/- 2 SDs) (Kitchen and Preston, 1995).

some individuals with severe FXI deficiency who do not bleed, and has not been detected in "bleeders" [43]. This mechanism would not explain the variability of bleeding tendency found within some families [18]. Researchers have reported cases of patients who have platelet defects in addition to FXI deficiency [44, 45]. A U.K. study found no abnormal bleeding times in 63 patients with FXI deficiency [19]; however, recent careful analysis of 27 patients from 18 families led to identification of 16 with various platelet defects [45].

Role of fibrinolysis at sites of injury

Surgical bleeding in FXI deficiency is most frequently provoked by dental extraction, tonsillectomy, adenoidectomy, nasal surgery, and prostatic surgery. These are areas with increased fibrinolysis, which clearly enhances the bleeding tendency [33, 46, 47]. However, severe bleeding has occurred after many other types of surgery including appendectomy [11, 31, 33, 48] and excision of breast lumps [30, 48]. Bleeding after childbirth is not usually a problem [12, 30, 33] although it has been reported in some studies, even with women with partial deficiency [13, 14, 19]. A review of 165 severely FXI-deficient individuals who underwent 120 procedures without replacement therapy demonstrated no excessive bleeding in 9 orthopedic procedures. Bleeding risk was low in surgery in areas with no increased fibrinolysis, but did occur in 49-67% of procedures in areas of high fibrinolysis [49].

In summary, inheritance of FXI deficiency is autosomal, affecting both men and women. Severe deficiency is measured as FXI:C level less than about 20 U/dL and partial deficiency as FXI:C level between 15-20 U/dL and the lower limit of the normal range. Most individuals with severe deficiency do not suffer from spontaneous bleeding, but are at risk of bleeding after surgery. A proportion of individuals with partial deficiency bleed excessively after challenge, but it is very difficult to identify in advance who is likely to bleed.

Racial Distribution

FXI deficiency is particularly common in Ashkenazy Jews, who are considered to be the descendants of Jews who left Jerusalem after the destruction of the temple in AD 70 and migrated to Poland and the Baltic states during the first century [50]. However, it has now been reported in most racial groups.

The frequency of partial deficiency among Ashkenazy Jews is 8% [51], making it one of the most common genetic disorders in this population. The high frequency suggests a heterozygote advantage, or linkage to some other favourable gene [52]. With this frequency, it is relatively common for two unrelated individuals with partial deficiency to marry and produce a child with severe deficiency. Severe deficiency can also occur in offspring where one parent has severe deficiency and the other partial deficiency.

The frequency of FXI deficiency in non-Jews is not known. In the U.K. about 7% of all patients with bleeding disorders on the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) national hemophilia database have FXI deficiency, many with no known Jewish ancestry [19]. This is more than the number of people with hemophilia B. Because both severe and partial FXI deficiencies are only revealed after an incident where blood does not clot, the condition is probably underdiagnosed. Recent analysis suggests that the C128X mutation (see below) is relatively common in the U.K. population, being found in 1-2% of individuals with no known bleeding problem [53].

Molecular Genetics

The FXI gene (designated *F11*) is located close to the gene for prekallikrein on chromosome 4 [52]. It is 23 kilobases in length with 15 exons and 14 introns. The first two exons do not code for a functional part of the molecule, exons 3 to 10 code for four tandem repeats (apple domains) and exons 11 to 15 code for the carboxyterminal containing the active site.

The first three *F11* gene mutations were described in six severely affected Ashkenazy Jews [54]. Several other mutations causing FXI deficiency have now been described, for example in [38] and [55-64]. A regularly updated list can be viewed at www.factorxi.org.

In contrast to most coagulation factor deficiencies, most mutations in *F11* are associated with failure to produce or reduced production of the active protein, with only a few related to production of dysfunctional molecules [16, 37, 38, 39].

While a variety of mutations have been identified in non-Jews, a restricted number of mutations (type II – E117X and type III - F283L) cause FXI deficiency in the Ashkenazy population. Type II (a stop codon in exon 5) and type III (a single base change in exon 9) mutations occur with equal frequency in the Ashkenazy population [51, 62]. People homozygous for the type II mutation have very low FXI:C levels (less than 1 U/dL), consistent with the failure to produce any protein. They are likely to bleed excessively from injuries and after all types of surgery. The type III mutation leads to defective dimer formation and secretion [65]. People homozygous for the type III mutation produce a low level of FXI (around 10 U/dL) and have a less severe bleeding tendency than those homozygous for the type II mutation. People who are compound heterozygotes for types II/III have an intermediate FXI:C level and clinical expression. There is no evidence of a difference in clinical expression between people heterozygous for the type II mutation and those with the type III mutation.

The restriction to two principal mutations and the history of the dispersion of Ashkenazy Jews is consistent with a founder effect in the population. Recently the type II (but not the type III) mutation has been found in Iraqi Jews but at a lower frequency (3.3%). This suggests that the type II mutation may have occurred before partition of the Jews [66]. Other mutations have mainly been described in individual families, but recently the same mutation (C128X) has been described in several families in the U.K. [53]. This is not a recognized hot spot for mutation, and haplotype analysis demonstrates that this is a founder effect. A similar population restriction has been observed for the C83R mutation found in the Basques [67], and a further group of unrelated families in France (Nantes) share the Q88X mutation [39].

Management of FXI Deficiency

It is clear that people with severe deficiency are commonly at risk of bleeding from surgical procedures in areas of high fibrinolytic activity, particularly tonsillectomy, and therefore appropriate measures must be taken to reduce the risk of bleeding. A review of one centre's experience demonstrated that bleeding occurred in 22 of 31 (71%) patients who underwent tonsillectomy without treatment. Of these, 12 of 14 (93%) of those with severe deficiency bled, while 10 of 17 (59%) with partial deficiency bled. In addition, 28 of 55 (51%) dental extractions were complicated by bleeding—15 of 25 (60%) patients with severe deficiency and 13 of 30 (43%) patients with partial deficiency [21]. This variability, together with the disadvantages associated with the various treatment modalities, makes managing FXI deficiency a challenge. The recent publication from Israel, however, suggests a more parsimonious use of replacement therapy in severely deficient patients is appropriate, determined by the site and type of surgery [49].

Therapeutic products available for the management of FXI deficiency

Fresh frozen plasma (FFP)
Plasma was used to treat the first known cases of FXI deficiency and was the main treatment until the development of FXI concentrates. The principle disadvantages of plasma are the large volumes required, allergic reactions, and the potential for transmission of infectious agents [47, 68].

The development of viral-inactivated products, either pooled solvent-detergent-treated or single-donor units treated with methylene blue, has made FFP safer. The solvent-detergent-treated product has been evaluated in eight patients with congenital bleeding disorders, including FXI deficiency. The calculated half-life of FXI:C was 45 hours, similar to standard FFP [69]. However, others have reported a rather variable FXI:C content in this product, with some batches containing only 35 to 50 U/dL [70]. Recent work indicates that it is possible to pasteurize pooled FFP (thawed at 30°C and then heated at 60°C for 10 hours), with preservation of 75 to 95% activity of factor XI [71]. As there are concerns about thrombogenicity in some

patients receiving FXI concentrates, there is clearly still a place for FFP.

FXI concentrates

Three FXI concentrates have been developed and tried in patients with FXI deficiency. Two of these are currently available and provide good treatment for suitably selected patients.

In 1991 an alarming report appeared from Israel describing disastrous results with a concentrate used in three patients [72]. Two showed coagulation activation with D-dimer production. One patient who received concentrate to cover coronary bypass grafting died post-operatively with occlusion of all grafts. Another died from post-operative hemorrhage. There were no details given of the content or manufacturing process of the concentrate, which has since been abandoned.

The other two products are different in manufacture and content, particularly with respect to antithrombin. Both are hemostatically effective and virally safe, but have been associated with evidence of coagulation activation and some thrombotic events, usually in association with pre-existing vascular disease.

Since 1984, a FXI concentrate has been available on a named-patient basis in the U.K. from Bio Products Laboratory (BPL, formerly the Plasma Fractionation Laboratory, Oxford). The BPL product is formulated with a high concentration of antithrombin (mean 102 IU/mL), which is thought to protect against any residual XIa. The concentrate is dry heated at 80°C for 72 hours in the final container to inactivate viruses. The first published review of its use reported on 31 invasive procedures in 30 patients whose age ranged from 7 to 71 years and demonstrated good hemostatic efficacy with no significant adverse events [73]. The mean FXI:C recovery was 91% of the injected dose (based on 62 measurements) and the mean half-life was 52 hours. Further *in vitro* work with the concentrate demonstrated some evidence of thrombogenicity, similar to prothrombin complex concentrates, in the Wessler venous stasis test (ligation of rabbit jugular veins at 30 seconds after the infusion of 200 U/kg of concentrate with examination of thrombus formation at 10 and 20 minutes) [74]. The addition of heparin to the concentrate (10 U/mL) resolved the problem. The product has included heparin since 1993.

Since the addition of heparin, however, four patients have been reported with serious thrombotic events, three fatal (two myocardial infarctions and one cerebrovascular accident), shortly after infusion [75]. All were elderly patients (aged 61 to 85 years) with evidence of pre-existing cardiovascular disease. Studies of other patients receiving six infusions of concentrate have now demonstrated that coagulation activation may occur (without clinical events) as indicated by elevations of fibrinopeptide A, thrombin-antithrombin complexes after all infusions, and prothrombin fragment 1+2 after four infusions. The highest elevations were seen in patients with pre-existing coagulation activation [76]. These findings suggest that the current animal models are not sufficiently sensitive to indicate the prothrombotic potential, probably because there is no satisfactory animal system with pre-existing activation (recipient factors).

More extensive experience with the BPL product was reported at the WFH congress in 1996 [77]. BPL has supplied concentrate for 273 patients. Data have been received for 229 treatment episodes in 161 patients aged 3 to 88 years; 53 patients were aged more than 60 years. Therapy was given to cover procedures on 191 occasions and for spontaneous or traumatic bleeds on 25 occasions (no data for 13 treatments). There were 21 adverse events in 19 patients, 12 of which were probably or definitely thrombotic. In addition to the four events previously reported [75], other events included two patients with pulmonary emboli, one with acute respiratory distress syndrome, one with chest pain, three with calf pain but no objective evidence of venous thrombosis, and one with transient asymptomatic disseminated intravascular coagulation. Two-thirds of doses given overall were higher than the 30 U/kg recommended, but there was no statistical correlation between the events and the dose given. The viral safety data are of limited value but no transmissions of HIV or hepatitis have been observed. The measurements of response and half-life are compatible with those in the original report [73].

A single-centre experience was reported in 2002 [78]. Seventy surgical episodes were evaluated in

43 patients (20 with severe deficiency) treated with the BPL product from September 1996 to September 2001. The median post-infusion FXI:C level was 65 U/dL. No thrombotic events were observed in this group.

The BPL product has been used in the U.S. in a study of elective surgery in 12 patients receiving 15 infusions [79]. The individuals were aged 24 to 81 years. One patient developed anaphylaxis and laboratory but not clinical evidence of disseminated intravascular coagulation (DIC). One patient had a pre-existing inhibitor. In all other patients the concentrate was used very successfully and was felt to be an important therapeutic option because of the small volume of infusion, viral safety, and the risk of inadequate levels that may be achieved using FFP.

Similar results were found with Hemoleven, a FXI concentrate used in France since 1993. Manufactured at Lille, Laboratoire Français du Fractionnement et des Biotechnologies (LFB), it contains 3 to 5 U/mL heparin/mL and 2 to 3 IU/mL of antithrombin, both of which are smaller amounts than in the BPL product [80]. *In vitro* testing showed no evidence of thrombogenicity in the Wessler model, but the concentrate is also associated with coagulation activation in laboratory tests, and clinical sequelae in some patients. Three patients were reported in 1995, one of which developed laboratory evidence of DIC with no clinical sequelae [81]. Coagulation activation was subsequently reported in two more patients, one with DIC [82]. One was a 19-year-old woman undergoing surgery for a pilonidal sinus and the other was a 69-year-old woman having a mastectomy for carcinoma of the breast. Both had elevation of prothrombotic markers, and the latter patient had a fall in platelet count and fibrinogen, although there were no clinical sequelae. After these cases were reported, the product was modified and C1 inhibitor added.

An update on the experience with the French product was provided at a meeting in December 1996 to discuss the management of FXI deficiency in light of the thrombotic problems being experienced with the available concentrates [70]. Thirty-one patients had been treated to cover 33 procedures, half with the modified concentrate. The ages ranged from 5 to 76 years and 22 patients had severe deficiency. Recovery (studied in 12 patients) was 80 +/- 16% of maximal theoretical and the half-life was 46 hours (range 32 to 52). A number of patients had elevated thrombotic markers, and thrombotic events complicated three infusions, one of which is described above. In all three cases the dose had exceeded 30 U/kg. A man with pre-existing coronary heart disease, diabetes, and hypertension developed DIC after 60 U/kg used to cover a hernia repair. It was resolved with therapy with low molecular weight heparin, but the patient developed a venous thrombosis and pulmonary embolus nine days after the last infusion of concentrate, and died six days later with renal failure and peritonitis. Another patient developed DIC followed by venous thrombosis and pulmonary embolus at 12 days. He recovered with treatment with anticoagulants. A review of experience with this product has now been published [83].

We can conclude that the LFB and BPL concentrates are hemostatically effective and free from viral transmission, but should be used with caution especially in elderly people with pre-existing cardiovascular disease and in individuals with pre-existing coagulation activation (e.g., pregnant or puerperal women, patients with malignant disease). However, when treating such patients there will be circumstances where the balance of risks still favours the use of these products, possibly in association with low molecular weight heparin prophylaxis. It should be noted that more than 40 individuals of more than 60 years of age have received the BPL product without adverse events. UKHCDO Haemophilia Centre Doctors' Organisation guidelines recommend that dosage does not exceed 30 U/kg and that the post infusion FXI:C level should not exceed 100 U/dL [84].

Some procedures, particularly dental extractions (see below), can be managed without the use of blood products even in patients with severe deficiency. Most people with severe deficiency are at risk of hemorrhage after procedures such as tonsillectomy or prostatectomy and will benefit from concentrate therapy. Concurrent use of tranexamic acid or other antifibrinolytic drugs should be avoided. Treatment with these products should only be carried out in centres experienced in the management of bleeding

disorders. It may be prudent to monitor thrombotic markers.

Fibrin glue
Because of the disadvantages of plasma products and anxiety about the thrombotic potential of FXI concentrates, some groups have used fibrin glue instead or as an additional modality. A group from Israel has published data on the successful use of fibrin glue in 80 patients with congenital bleeding disorders undergoing 135 dental extractions without blood product replacement; seventeen extractions were performed in 13 patients with FXI deficiency [85]. The glue (Beriplast®, Centeon) is applied through a pair of syringes, one containing calcium and thrombin, the other containing fibrinogen, FXIII, and aprotinin.. More recently it has been shown that antifibrinolytic drugs alone are sufficient for dental work (see below), and the Israeli group now uses fibrin glue either alone or in association with FFP for one to three days for other surgical procedures such as circumcision and hernia repairs (Martinowitz, personal communication).

Antifibrinolytic drugs
Antifibrinolytic drugs are effective and "concentrate sparing" in patients with hemophilia A. They are an important adjunct in patients undergoing surgery in areas of the body prone to increased fibrinolysis such as the oral cavity, bladder, and uterus. Studies have demonstrated that antifibrinolytic drugs alone are sufficient to cover dental extractions in patients with severe FXI deficiency [86]. Nineteen patients with FXI levels of less than 14 U/dL were given oral tranexamic acid starting 12 hours before surgery and continuing for 7 days afterwards. Fourteen had a history of bleeding after surgery and five had bled after trauma. One patient had some oozing on day 3 which stopped without intervention. No other bleeding complications were observed, demonstrating this to be a highly effective form of treatment.

Desmopressin (DDAVP)
Desmopressin has been used in a variety of bleeding disorders since the discovery that it raises FVIII:C and VWF levels. It is a well-established treatment for mild hemophilia A and VWD. More recently, it has been advocated in some platelet disorders [87]. If some patients with partial FXI deficiency bleed because they have mild VWD or have VWF levels towards the lower end of the normal range, then DDAVP might be effective. To date there is very little experience with the use of DDAVP in FXI deficiency. One group has reported success in two patients with previous bleeding histories who received DDAVP infusions before carpal tunnel surgery (baseline FXI:C levels of 34 and 39 U/dL, normal FVIII:C and VWF levels, and normal bleeding times) [88]. The FXI:C levels rose by 15 to 20 U/dL and the FVIII:C and VWF levels rose considerably. The patients experienced no bleeding, but it is not clear whether this was related to therapy. A more convincing case was reported where a 9-year-old girl with baseline FXI:C of 8% bled post-operatively; this ceased with DDAVP, which interestingly was associated with an increase in FXI:C to 31% and FVIII:C to 290%. [89]. The advantages of DDAVP are safety and ease of use, but more experience is required to establish whether or not it has a role in managing FXI deficiency.

Recombinant Factor VIIa (rVIIa)
The successful use of rVIIa has been reported in isolated cases, including those with inhibitors. A prospective study of rVIIa use in elective surgery commenced in November 2001. Normal hemostasis was achieved in all 15 procedures studied in 14 patients undergoing minor or major surgery. This is not a licensed use of this product. However, one elderly patient with a previous myocardial infarction died from a cerebrovascular event [90]. This product is therefore not recommended for use in FXI deficiency apart from possibly in the presence of inhibitors.

Inhibitors in Factor XI Deficiency

There is little literature concerning the development and management of FXI antibodies in individuals with congenital deficiency, although such antibodies are a recognized complication of autoimmune disease. One reason for the infrequent presence of inhibitors may be that many people with factor XI deficiency never receive treatment with plasma products. Inhibitors are particularly likely to develop in people who are homozygous for the type II mutation. Inhibitors developed in a third

of such patients (7/21) who had previously been exposed to plasma [91]. Some inhibitors are associated with residual FXI activity and may be treated successfully with plasma products. Others cannot be overcome and have been successfully treated with products used successfully in patients with antibodies to FVIII and IX, i.e., prothrombin complex concentrates or rVIIa. Patients with severe deficiency and inhibitors have been reported with no spontaneous bleeding.

FXI antibodies can cause significant inhibition and clinical problems [73, 78, 92-96]. Therefore, it is important that prior to elective surgery where plasma products are used, all patients are screened for inhibitors. Plasma-derived products should perhaps be avoided if possible in those known to be homozygous for the type II and other mutations that lead to a "stop" codon and therefore a complete absence of FXI:C in the plasma.

Neonates

Spontaneous bleeding, including spontaneous intracranial hemorrhage, in the neonate has not been reported. Serious bleeding may follow circumcision of severely deficient infants. At-risk neonates should have their FXI:C checked on a cord blood sample and if severely deficient, circumcision should be delayed for six months. If the level remains under 10 U/dL, the procedure should be performed under cover of FFP. Infants with levels greater than 10 U/dL may be managed with tranexamic acid.

Conclusion

Optimal management of patients with FXI deficiency requires attention to a number of features in addition to the FXI level. It is important to establish whether an individual with partial deficiency has a bleeding tendency or not, and whether additional factors are making a significant contribution. The assessment should include measurement of FVIII:C and VWF levels, possibly the bleeding time, and some measure of platelet function (aggregometry or use of the platelet function analyser). Planning for surgery and dental extractions needs to take into account the nature of the procedure in addition to the host factors. Possible alternatives to plasma and FXI concentrates should be considered, but concentrate is indicated when the risk of significant bleeding is high. If concentrate is used, elderly patients need to be informed of the potential risk of thrombosis in the presence of pre-existing vascular disease. However, the risk of serious hemorrhage will justify the use of concentrate in many situations.

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