FACTOR XI DEFICIENCY

Factor XI is a zymogen of an active serine protease (FIXa) in the intrinsic pathway of blood coagulation that activates FIX (Fig. 141-1). There are two pathways for the formation of FXIa. In an aPTT-based assay, the protease is the result of activation by FXIIa in conjunction with high-molecular-weight kininogen and kallikrein. In vivo data suggest that thrombin is the physiologic activator of FXI. The generation of thrombin by the tissue factor/factor VIIa pathway activates FXI on the platelet surface that contributes to additional thrombin generation after the clot has formed and thus augments resistance to fibrinolysis through a thrombin-activated fibrinolytic inhibitor (TAFI).

Factor XI deficiency is a rare bleeding disorder that occurs in the general population at a frequency of one in a million. However, the disease is highly prevalent among Ashkenazi and Iraqi Jewish populations, reaching a frequency of 6% as heterozygotes and 0.1–0.3% as homozygotes. More than 65 mutations in the FXI gene have been reported, whereas fewer mutations (two to three) are found among affected Jewish populations.

Normal FXI clotting activity levels range from 70 to 150 U/dL. In heterozygous patients with moderate deficiency, FXI ranges from 20 to 70 U/dL, whereas in homozygous or double heterozygote patients, FXI levels are <1–20 U/dL. Patients with FXI levels <10% of normal have a high risk of bleeding, but the disease phenotype does not always correlate with residual FXI clotting activity. A family history is indicative of the risk of bleeding in the propositus. Clinically, the presence of mucocutaneous hemorrhages such as bruises, gum bleeding, epistaxis, hematuria, and menorrhagia are common, especially following trauma. This hemorrhagic phenotype suggests that tissues rich in fibrinolytic activity are more susceptible to FXI deficiency. Postoperative bleeding is common but not always present, even among patients with very low FXI levels.

FXI replacement is indicated in patients with severe disease required to undergo a surgical procedure. A negative history of bleeding complications following invasive procedures does not exclude the possibility of an increased risk for hemorrhage.

TREATMENT FACTOR XI DEFICIENCY

The treatment of FXI deficiency is based on the infusion of FFP at doses of 15–20 mL/kg to maintain trough levels ranging from 10 to 20%. Because FXI has a half-life of 40–70 h, the replacement therapy can be given on alternate days. The use of antifibrinolytic drugs is beneficial to control bleeds, with the exception of hematuria or bleeds in the bladder. The development of an FXI inhibitor was observed in 10% of severely FXI-deficient patients who received replacement therapy. Patients with severe FXI deficiency who develop inhibitors usually do not bleed spontaneously. However, bleeding following a surgical procedure or trauma can be severe. In these patients, FFP and FXI concentrates should be avoided. The use of PCC/aPCC or recombinant activated FVII has been effective.

RARE BLEEDING DISORDERS

Collectively, the inherited disorders resulting from deficiencies of clotting factors other than FVIII, FIX, and FXI (Table 141-1) represent a group of rare bleeding diseases. The bleeding symptoms in these patients vary from asymptomatic (dysfibrinogenemia or FVII deficiency) to life-threatening (FX or FXIII deficiency). There is no pathognomonic clinical manifestation that suggests one specific disease, but overall, in contrast to hemophilia, hemarthrosis is a rare event and bleeding in the mucosal tract or after umbilical cord clamping is common. Individuals heterozygous for plasma coagulation deficiencies are often asymptomatic. The laboratory assessment for the specific deficient factor following screening with general coagulation tests (Table 141-1) will define the diagnosis.

Replacement therapy using FFP or prothrombin complex concentrates (containing prothrombin, FVII, FIX, and FX) provides adequate hemostasis in response to bleeds or as prophylactic treatment. The use of PCC should be carefully monitored and avoided in patients with underlying liver disease, or those at high risk for thrombosis because of the risk of DIC.

FAMILIAL MULTIPLE COAGULATION DEFICIENCIES

There are several bleeding disorders characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized, and they provide new insights into the regulation of hemostasis by gene-encoding proteins outside blood coagulation.

Combined Deficiency of FV and FVIII Patients with combined FV and FVIII deficiency exhibit ~5% of residual clotting activity of each factor. Interestingly, the disease phenotype is a mild bleeding tendency, often following trauma. An underlying mutation has been identified in the endoplasmic reticulum/Golgi intermediate compartment (*ERGIC-53*) gene, a mannose-binding protein localized in the Golgi apparatus that functions as a chaperone for both FV and FVIII. In other families, mutations in the multiple coagulation factor deficiency 2 (*MCFD2*) gene have been defined; this gene encodes a protein that forms a Ca^{2+} -dependent complex with *ERGIC-53* and provides cofactor activity in the intracellular mobilization of both FV and FVIII.

Multiple Deficiencies of Vitamin K–Dependent Coagulation Factors Two enzymes involved in vitamin K metabolism have been associated with combined deficiency of all vitamin K–dependent proteins, including the procoagulant proteins prothrombin, VII, IX, and X and the anticoagulant proteins C and S. Vitamin K is a fat-soluble vitamin that is a cofactor for carboxylation of the gamma carbon of the glutamic acid residues in the vitamin K–dependent factors, a critical step for calcium and phospholipid binding of these proteins (Fig. 141-2). The enzymes γ-glutamylcarboxylase and epoxide reductase are critical for the metabolism and regeneration of vitamin K. Mutations in the genes encoding the γ-carboxylase (GGCX) or vitamin K epoxide reductase complex 1 (VKORC1) result in defective enzymes and thus in vitamin K–dependent factors with reduced activity, varying from 1 to 30% of normal. The disease phenotype is characterized by mild to severe bleeding episodes present from birth. Some patients respond to high doses of vitamin K. For severe bleeding, replacement therapy with FFP or PCC may be necessary to achieve full hemostatic control.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease

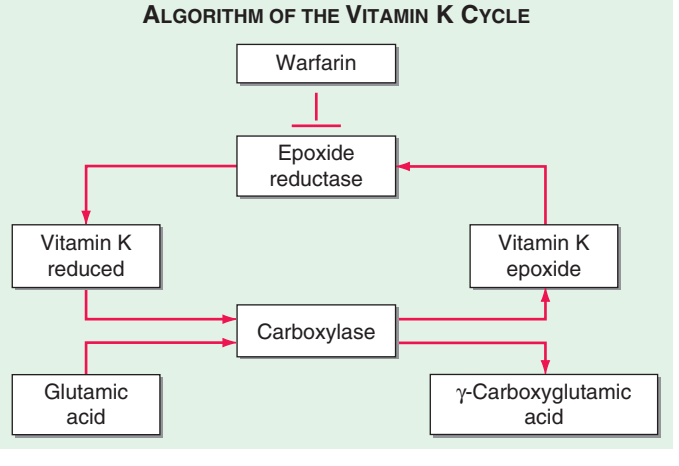

FIGURE 141-2 The vitamin K cycle. Vitamin K is a cofactor for the formation of γ-carboxyglutamic acid residues on coagulation proteins. Vitamin K–dependent γ-glutamylcarboxylase, the enzyme that catalyzes the vitamin K epoxide reductase, regenerates reduced vitamin K. Warfarin blocks the action of the reductase and competitively inhibits the effects of vitamin K.