ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Treatment of Factor XI Deficiency

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H&O How does factor XI deficiency differ from the classic hemophilias?

LA In patients with factor VIII or factor IX deficiency, it is possible to predict the severity and phenotype of the disease based on factor levels. For example, in patients with factor VIII deficiency, those with less than 1% of the factor have severe disease, those with 2–5% of the factor have moderate disease, and those with 5–50% of the factor have mild disease. In factor XI deficiency, however, the phenotype does not in any way follow the laboratory level of the factor. For example, there are many people with no factor XI who do not bleed excessively, either spontaneously or while undergoing surgical intervention. There are patients with factor XI deficiency of 25–30% who bleed spontaneously or while undergoing surgery. The amount of factor XI needed to prevent a bleeding episode in a patient prone to bleeding is not known.

H&O How common is factor XI deficiency?

LA We do not have very good figures for prevalence. It is a rare bleeding disorder. It is a disease that is most frequently seen in Ashkenazi Jews; therefore, in the United States, places like Florida, New York, Chicago, and Los Angeles will have a reasonable cohort of patients. Factor XI deficiency is also seen in Asians, but with a phenotype that is usually so mild it may go unnoticed even in patients who are bleeders, because spontaneous bleeding is not common, as it is in other types of hemophilia. Factor XI deficiency is usually diagnosed because a patient has a family member with the disease. This condition is genetic and passes as a dominant trait, although the rate of mutation is not clearly known. Factor XI deficiency is not linked to the X chromosome, and there are men and women with this disease. Patients who are scheduled to undergo surgery are screened using bleeding coagulation tests to ensure they are not at risk of bleeding.

H&O What are the diagnostic criteria for factor XI deficiency?

LA Patients with factor XI deficiency have normal prothrombin times. Therefore, their international normalized ratio is normal. All patients with a hemophilia factor deficiency, no matter what the phenotype, have a prolonged partial thromboplastin time (PTT). A prolonged PTT in somebody who is not bleeding is interesting. It could be factor XII deficiency—which is rarely, if ever, a bleeding disorder—or it could be a case of factor VIII or factor IX deficiency that is mild enough to be clinically inapparent. The laboratory evaluation must include all those assays. A patient with prolonged PTT who has bled during past surgery must be evaluated for all the factor deficiencies, including factor VIII, factor IX, factor XI, and von Willebrand disease.

H&O Which patients with factor XI deficiency are more likely to bleed excessively during surgery?

LA When trying to identify a patient who will bleed excessively, the most important determinant is family history. For example, if a patient has a long PTT and has never experienced trauma or a surgical intervention that might make him or her bleed, but there is family history of factor XI deficiency, then excessive bleeding is likely.

There are other key issues to consider when determining whether or not a patient might bleed excessively. One is bleeding during oral surgical manipulation because the oral cavity is flooded with saliva that contains fibrinolytic

material. Such procedures include tonsillectomy, tooth extraction, and implantation of paraphernalia into the tongue. Bleeding from the oral cavity should raise strong suspicions that the patient is a bleeder. Excessive bleeding during other types of surgical procedures is also clear evidence that the patient is a bleeder. Blood in the urine is another indication.

H&O In the United States, how are patients with factor XI deficiency prepared for surgery?

LA Patients who have a long PTT or XI deficiency should undergo consultation with a hematologist experienced with factor XI deficiency if they must undergo surgery. I see many of these patients because they are scheduled to undergo a surgical procedure (eg, gynecologic surgery, cardiac surgery, hernia repair, pacemaker implantation).

If the patient is perfectly asymptomatic and has no family history of bleeding, the approach will depend on the procedure. If the patient will receive simple stitches, no intervention may be necessary. If the procedure is more major—such as opening up a cavity or going into the brain—it behooves one to correct the factor to as high a level as can be achieved without fluid overload, which happens with too much plasma.

Little is known as to how much the factor must be raised. In factor XI deficiency patients who need surgery, the following kind of regimen may prevent excessive bleeding: 2 units of fresh-frozen plasma the night before the procedure—since the half-life is very long—2 units prior to the procedure, and 2 units the day after. If the surgery is performed in the bladder or gastrointestinal tract, where there is a slough, on the eighth to tenth day, 2 more units of fresh-frozen plasma are administered because that is when the scar tissue comes off and bleeding recurs. Some patients, such as women who have had multiple pregnancies, will develop an allergic reaction to plasma; 100 mg of intravenous hydrocortisone sodium succinate and diphenhydramine are very salutary. We usually administer diphenhydramine to men who have not received plasma before, to be sure to avoid an allergic reaction. On the other hand, it is not unheard of for patients to experience an allergic or anaphylactic reaction to the plasma. These patients must be pretreated for days before the procedure with high-dose steroids, which should be maintained during the plasma treatment. This approach has its own negative side effects, such as the risk of potential infection.

H&O What other options for treatment exist?

LA Factor XI concentrates are produced by the French (Hemoleven, LFB Biomedicaments) and the English (FXI concentrate, Bio Products Laboratory); Canadians import the French version. In the United States, we do not manufacture a factor XI concentrate because the market is too small. How does the concentrate differ from plasma? With the concentrate, it is possible to predict the amount of factor XI that will be given and the level that will be achieved. The concentrates are virally inactivated and have essentially no chance of transmitting a virus.

In the United States, we are handicapped by not having a concentrate. There is now a compassionate use program with which the French factor XI concentrate can be used in the United States. I have used it to achieve very good levels of factor XI in my patients. My colleagues and I have published several articles on the English and French factor XI concentrates. They are superb products, but they are difficult to obtain in the United States. To obtain a license in the United States to use these products, it is necessary to be a part of a clinical trial and to receive approval for your institution's plasmapheresis program. We need an easier way to utilize either the French or the English product in this country without all of the difficulties of importation, payment, compassionate use, and approval by the institution—all of which is an enormous hassle for clinicians, particularly those who may be less familiar with factor XI deficiency.

Suggested Readings

Aledort LM, Goudemand J, and the Hemoleven Study Group. United States' factor XI-deficiency patients need a safer treatment. *Am J Hematol*. 2005;80:301-302.

Kadir RA, Kingman CE, Chi C, et al. Screening for factor XI deficiency amongst pregnant women of Ashkenazi Jewish origin. *Haemophilia*. 2006;12:625-628.