

Factor XIII Deficiency One of Rarest Bleeding Disorders

Factor XIII needed to stabilize clots

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Update: [The Food and Drug Administration \(FDA\) approved Corifact](#), the first factor treatment for factor XIII deficiency available in the US, on February 17, 2011. Corifact is already available in 12 other countries under the name [Fibrogammin P[®]](#).

Kathy Stewart, co-president of the [Central Ohio Hemophilia Foundation](#) of Worthington, Ohio, is the mother of three grown children with factor XIII deficiency. - Factor XIII, also known as **fibrin stabilizing factor**, stabilizes the clot that forms when a person bleeds. A clot, made up of many clotting proteins and platelets, acts like a patch to stop bleeding. When some of the clotting proteins, called coagulants, are missing or not properly formed, the patch may not work effectively and the bleeding may continue. Without factor XIII, the clot will still form but it will be easily broken down, causing the bleeding to start again.

Factor XIII deficiency is one of the rarest bleeding disorders, affecting one in 5 million live births in the world, according to the [National Hemophilia Foundation](#). In contrast, **hemophilia A** affects one out of every 5,000 male births and **hemophilia B**, one out of 25,000 male births.

Kathy knows firsthand the difficulties of getting a proper diagnosis. "My son Nelson was not diagnosed until after his sister, Vanessa, was born," she says. "He had bleeding from a circumcision for more than a week that resulted in his being admitted to the hospital. All the tests they did showed no evidence of hemophilia. Finally, they gave him whole blood, which stopped the bleeding."

"Factor XIII stabilizes blood clots after they have already formed," says Bernard Silver, MD, staff physician in the hematology department at the Cleveland Clinic in Ohio. "This makes them durable and solid."

This is one major difference from the more common **bleeding disorders**. In hemophilia A and B, problems occur earlier in clot formation, and clots are not able to form at all.

"This deficiency is genetic, and both parents must have the gene to pass it along to the baby," says Diane Nugent, MD, medical director of [Hematology and Blood Donor Services](#) at the Children's Hospital of Orange County in Orange, California. "Unlike hemophilia A and B, which are passed along via the X sex gene to boys, factor XIII deficiency is seen equally in both boys and girls."

Umbilical Cord Bleeding May Be the First Clue

Bleeding from the umbilical cord is often the first symptom of **factor XIII deficiency**. Others include excessive bruising, nose and mouth bleeds, bleeding under the skin and bleeding into muscles. The bleeding is often delayed—that is, it occurs several days after surgery or trauma because clots still form normally, but the lack of factor XIII prevents clots from strengthening. A frequent and often devastating symptom is bleeding into the brain, also known as **intracranial hemorrhage**. Female carriers may have frequent miscarriages.

Because factor XIII holds a clot together after formation, most standard laboratory tests for clotting show normal results in a factor XIII-deficient person. The diagnosis is often made by the presence of symptoms and by eliminating other potential causes of bleeding. Specific tests for factor XIII and clot stability confirm the diagnosis.

When Kathy brought Nelson to the hospital after he had been bleeding for more than a week, the doctors told her it was a freak occurrence and that there was nothing to worry about. When Vanessa was born two years later, she bled from the umbilical cord, and an important part of the puzzle fell into place.

“This deficiency is unique in that virtually all of affected newborns have umbilical cord bleeding,” says Marilyn Manco-Johnson, MD, director of [Mountain States Regional Hemophilia and Thrombosis Center](#) in Denver. “One patient in four with the disorder will experience bleeding into the brain. This is much higher than rates seen in hemophilia A or B.”

Establishing the severity of the deficiency can be difficult. “One of the challenges to diagnosing this deficiency is that we don’t yet have a good test for those with 10% factor or less,” says Nugent. “This means there is not an exact number that we can link severity to, so we usually do that based on presentation. Those with frequent bruising and bleeding, especially into the brain, are considered severe while less bruising and bleeding only following a trauma like surgery are considered moderate. People who seldom bleed are considered mild.”

Factor XIII Deficiency Treatments Available

Two treatments for factor XIII deficiency are available in the US. Both are made from plasma, the liquid part of the blood. Although only factor XIII is needed, all the factors and proteins in plasma are included.

In the first treatment, fresh plasma is collected, frozen and stored until used. The second treatment, **cryoprecipitate**, requires that the plasma be frozen and then slowly thawed. This slow thaw causes the factor to separate from the plasma and is generally more concentrated than **fresh frozen plasma**. Unlike other forms of treatment, cryoprecipitate does not go through processes that can kill viruses in the blood and reduce the risk of transmitting these types of diseases. Because the treatments are considered blood transfusions, patients or their family members cannot infuse at home. Trips to the doctor or the emergency room are necessary.

“With both of these treatments, there are some concerns that patients should know about,” says Silver. “All products that come from plasma contain proteins and factors that are different from those naturally produced by the person receiving the treatment. This can cause an allergic, or what we call a hypersensitivity, reaction in some people.”

In addition, there is a small chance that viruses, such as those that cause hepatitis and AIDS, could be inadvertently transmitted in the plasma, along with the factors. All three medical experts interviewed for this story said that donors are screened, but that there is still what they called a “low, but not zero” risk of contamination.

A third treatment, Fibrogammin P[®], is available in Europe, Canada and Japan. It is still in the final stages of clinical trials in the United States and is only available through doctors participating in the Investigational New Drug study. This means the medication can only be given at larger medical centers and other places that have experience with the patient safeguards required by the [FDA](#). *Update: On February 17, 2011, the FDA approved Fibrogammin P[®], known as Corifact, for use in the US.*

This treatment is also made from plasma. Unlike the other treatments, only factor XIII remains and the medication undergoes an additional cleaning step, further reducing the chance of virus transmission. There is also a recombinant form of factor XIII undergoing study; that formulation carries no real risk of viral transmission.

“My children have also been prescribed Fibrogammin P[®], and it is much easier to use,” says Kathy. “It is easily stored in the refrigerator and can be given in the home without having to involve a doctor or nurses, so it saves trips to the emergency department.”

The available treatments are all used prophylactically to prevent bleeding episodes. “It is very important that both physicians and patients understand that prophylaxis is very feasible in this disorder and that it can prevent intracranial hemorrhage or other life-threatening events,” says Manco-Johnson. “Because factor XIII lasts so long in the bloodstream, treatment is usually monthly. Also, as little as 5% of normal can still prevent bleeding.”

Factor XIII Deficiency Research and Support Difficult

Because so few people have factor XIII deficiency, it is difficult to find information on it and doctors who specialize in treating it. Silver, for example, only knows of two families with the disorder in Northeastern Ohio. Nugent treats three patients—out of the 5 million people who live in Orange County, California.

“Any hemophilia treatment center [HTC] or the hematology department of a major medical center with a specialist in coagulation disorders will be able to treat factor XIII deficiency,” says Silver.

However, treatment for the disorder may not always be well understood by healthcare workers outside the HTCs. When Kathy’s youngest son, Mark, fell and had bleeding inside his head, treatment was delayed. The pediatrician, who was unfamiliar with factor XIII deficiency and its risk of intracranial hemorrhage, looked for an ear infection and the flu.

“Problems continued while the kids grew up,” says Kathy. “I have gotten several articles on this that I give to new doctors. I also have a list made up by the HTC that tells emergency room or other doctors how much fresh, frozen plasma is needed over what time period.”

Individuals with the disorder are spread out across the US, making information and support specific to the disease hard to find. HTCs are generally not able to provide support groups for these patients and their families, who typically end up being placed in more general groups.

Still, much of the networking and education about this deficiency fall to those most affected by it. Kathy gathered information on other medical treatments for factor XIII deficiency from a person she contacted through the [National Organization for Rare Disorders](#) (NORD). She also wrote letters to HTCs and NHF chapters asking if they knew of any families with the deficiency and asking them to pass her name along.

Rare Bleeding Disorders Database

To more efficiently gather information on patients with factor XIII deficiency and other rare bleeding disorders, the [Centers for Disease Control and Prevention](#) (CDC) is working with HTCs in the US on a patient registry. The registry may also be linked with a similar database in Europe to further increase the information flow on these rare disorders.

“This will help us accurately assess the number of persons with factor XIII deficiency and enable researchers to more effectively estimate the number of patients for treatment trials, new tests and other important research,” says Manco-Johnson. “The cataloging of gene mutations may help develop gene therapies.”

Nugent says, “No one can step up and develop treatments if they can’t even know how many patients there are and what kind of bleeding events we are trying to prevent.”

The database will collect information on patient demographics, family histories, treatments and patient responses. Other details of interest include incidence of complications, such as what triggers bleeding episodes.

This work may soon result in changes to a major data collection tool used at HTCs nationwide. The Universal Data Collection Tool (UDCT) is a standardized questionnaire developed in conjunction with the CDC that is used at all HTCs. Started as a method to gather information on the joint problems associated with hemophilia A and B, the UDCT has broadened the understanding of these diseases. Researchers hope it eventually will do the same for rare bleeding disorders.

“The UDCT has been incredibly useful in finding what things can impact outcomes in our patients,” says Nugent. “Now we may be able to develop hard information on how well treatments work and what other things may help or interfere with treatments.”

Learn More ...

- Visit the [factor XIII deficiency](#) section of the NHF Web site. You can also find a report on the [NORD](#) Web site.
- Other sources include the [Canadian Hemophilia Society](#), which has a publication that can be downloaded free.
- International [Factor XIII Registry Database](#).

Tests for Factor XIII Deficiencies

Factor XIII does not affect the early parts of the clotting process; it is responsible for the strength of the clot after it is formed. Because of this, most standard tests for blood clotting cannot be used because they produce normal results that do not indicate factor XIII deficiency.

Tests include:

- A test of **clot stability** is the most common screening method for factor XIII deficiency. In this test, a blood sample is taken and allowed to clot; the formed clot is suspended in a solution. If factor XIII is present, the clot will remain stable after 24 hours. If not, the clot will dissolve quickly, sometimes within minutes.

This test result is positive when no factor XIII is present. However, factor XIII levels as low as 1% to 3% may be enough to stabilize the clot. Therefore, in patients with milder deficiencies or in those with recent transfusions, the results of the test may still be normal.

- The next step is usually an **assay test for factor XIII**. Two tests measure the activity of factor XIII by measuring the amount of certain chemicals that are produced when the factor is working correctly.
- **Enzyme-linked immunosorbent assay (ELISA)** is another test often used to find levels of factor XIII in the blood. When the factor is present in the sample, the test solution changes color, indicating a positive test result.