Literature Review

Hemophilia C in Women

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Abstract

Factor XI (FXI) deficiency (hemophilia C or Rosenthal syndrome) is a genetically-transmitted disease usually inherited in an autosomal recessive pattern associated with genetic defects in the FXI gene. It affects both genders equally, but studies show that the disorder is more common in Ashkenazi Jews. People with hemophilia C do not have spontaneous bleeding, symptoms like uncontrollable or prolonged bleeding, epistaxis, hematuria or bruising occur after serious injuries, major surgeries or after giving birth. In female it may cause menorrhagia. Unless there's an undergoing surgery or an injury that may cause severe bleeding, people with hemophilia C do not require treatment. Fresh frozen plasma, anticoagulant medication or birth control might reduce the risk of excessive bleeding.[1]

Introduction and etiology

Factor XI (FXI), also known as plasma thromboplastin antecedent (PTA), is a key player in the intrinsic pathway of the coagulation cascade. It acts by activating FIX, which, in turn, contributes to the generation of thrombin and the formation of a stable blood clot.

Factor XI is a dimeric serine protease, which is composed of chains that each weigh 80,000 Da. Factor XIIa activates factor XI and factor IX in the original intrinsic pathway of blood coagulation. Also, thrombin directly activates factor XI, and this direct activation may be more important than the activation due to factor XII. Recently, it has been shown that thrombin activation of factor XI is triggered by polyphosphate release from activated platelets. These molecules provide a template for assembly of factor XI and factor IX. Patients with factor XII deficiency, even severe deficiency, do not necessarily have a tendency to bleed. Therefore, the absence of factor XII appears to be irrelevant to factor XI.

Factor XI is a zymogen that, on activation, undergoes conversion to a serine protease that leads to activation of factor IX, followed by thrombin generation. The sustained generation of thrombin also leads to the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which impairs the conversion of plasminogen to plasmin. Thus, factor XI serves as a procoagulant and an antifibrinolytic agent, and the lack of factor XI in plasma results in a tendency to bleed. People with severe factor XI deficiency have a lower incidence of ischemic stroke.[2]

Factor XI does not play a role in the complement or kinin pathways, however, it has been demonstrated to contribute to the activation of fibrinolysis. The primary inhibitor of factor XIa is alpha-1 antitrypsin, responsible for approximately two-thirds of its inhibition. The remaining inhibition is attributed to C1 esterase inhibitor, antithrombin III, and alpha-2 antiplasmin.[2]

In individuals with a significant deficiency of factor XI, bleeding typically occurs in response to injury, particularly when trauma involves tissues abundant in fibrinolytic activators, such as the oral mucosa, nasal tissues, or the urinary tract. Unlike individuals with severe hemophilia A or B, those with a major deficiency of factor XI do not experience spontaneous bleeding events.

Factor XI deficiency is an uncommon autosomal bleeding disorder linked to genetic anomalies within the FXI gene. The gene for factor XI is near the gene for prekalikrein on the distal arm of chromosome 4 (4q35). It is 23 kb, with 15 exons and 14 introns. Factor XI is synthesized in the liver and circulates in the plasma as a complex with high-molecular-weight kininogen. Factor XI has a half-life of about 52 hours.[2] This condition exhibits significant heterogeneity, manifesting as varying tendencies towards bleeding and diverse causal mutations within the FXI gene. It can be classified into two main categories: cross-reacting material-negative (CRM-) FXI deficiency, characterized by reduced FXI levels, or cross-reacting material-positive (CRM+) FXI deficiency, marked by impaired FXI function. The FXI mutation database has reported an increasing number of mutations, primarily impacting the serine protease (SP) domain of the FXI protein. The functional analysis of these mutations contributes to a deeper understanding of the molecular mechanisms underpinning FXI deficiency.[3]

Epidemiology

Hemophilia C is more common in certain populations and geographic regions. It has a higher prevalence among Ashkenazi Jews of Eastern European descent, living in Israel, with an estimated frequency of 8-9% of Ashkenazi Jews being carriers of the genetic mutation that causes factor XI deficiency. Two mutations are predominant in this group: type II (Glu117Stop), about 30% of homozygous patients develop inhibitors for FXI and type III (Phe283Leu).[4] In other populations, the prevalence is generally lower, affecting 1out of 100.000 people worldwide. Both genders are equally affected.[5] Moreover, people of any age group can be affected. To note is the fact that normal infants younger than age 6 months have low levels of factor XI because of the time required for factor XI to reach normal levels observed in adults. After this is reached, factor XI levels do not change with age.[2]

Diagnosis

It is not easy to diagnose hemophilia C. The genetic analysis could be helpful to determine which mutation caused the factor XI deficiency. Imaging studies bring no further information about the pathology unless, there is an actual bleeding happening, it might help to evaluate the extent of the bleeding. Most important for the diagnosis are the laboratory studies which include: complete blood count (CBC), measurement of factor XI levels, measurement of factor VIII and von Willebrand factor, prothrombin time (PT), thrombin time (TT) which are normal and activated partial thromboplastin time (aPTT) which is usually prolonged. Rosenthal Syndrome may coexist with other deficiencies so as assays of other clotting factors and platelet function may be needed. The deficiency is categorized as major when the factor XI levels are 15-20 U/dl or lower in patients with at least 2 FXI gene mutations. Individuals with partial deficiency, generally heterozygotes with a single FXI gene mutation, have levels of 20-60 U/dl. Unlike other coagulation problems, the severity and chance of bleeding correlates poorly with factor levels.[2]

Differential diagnosis

The diagnosis of Hemophilia C is primarily established through laboratory testing, which involves demonstrating insufficient levels of factor XI activity. While other bleeding disorders may present with similar clinical symptoms, the differentiation between these conditions is largely reliant on laboratory results. Congenital hemophilia A and B are clinically similar but unlike hemophilia C these conditions are distinguished by the occurrence of deep and spontaneous bleeding episodes. A similar clinical picture has the von Willebrand disease, which results from deficiency or abnormal function of this factor, which role is to initiate platelet adhesion in primary clot formation and also to stabilize factor VIII. Any other coagulation factor deficiency may present with a variety of bleeding patterns, similar to the Rosenthal syndrome.[6]

Treatment and management

Because the severity of bleeding cannot be predicted by the levels of factor XI in the blood, the treatment and management of hemophilia C could be questionable. However, many options have been found to prevent the excessive bleeding. As the highpoint of this article is the FXI deficiency in

women, treatment and management options will be discussed in correlation with gynecological procedures and surgeries.

Prophylactic therapy is advised for women with severe factor XI deficiency undergoing surgery. However, the guidance for heterozygotes with mildly reduced activity levels and no prior surgical history is less straightforward. Studies show that individuals with further factor deficiencies like low von Willebrand factor, thrombomodulin and von Willebrand ristocetin cofactor were more likely to bleed during surgical procedures and were categorized as "bleeding" individuals.[7,8] Another study explored thrombin generation in two groups: one consisting of 9 individuals with a documented history of bleeding and the other comprising 15 subjects without any bleeding episodes during previous traumatic events or surgical procedures. Regardless of their factor XI activity levels, individuals with a history of bleeding exhibited significantly reduced *in vitro* thrombin generation characteristics. These included extended lag time, reduced peak thrombin levels, and diminished thrombin generation velocity. These values were lower than those observed in normal control subjects and factor XI-deficient patients who did not have a history of clinical bleeding. This raises the possibility of utilizing thrombin-generation assays as a predictive tool for assessing bleeding risk.[7,9]

The most common management when it comes to factor XI deficiency-related bleeding is the **fresh frozen plasma FFP**, which may be used also as prophylaxis. The daily administration dose is about 20 ml plasma/kg, with a factor goal between 20 and 50%, depending on the nature of the procedure. Potential side effects of FFP transfusion include transfusion-associated circulatory overload, transfusion reaction, alloimmunization, anaphylaxis, and transfusion-related acute lung injury.[7]

Desmopressin, which is a synthetic analog of vasopressin, is used as a hemostatic agent in various bleeding disorders. These include conditions such as von Willebrand disease, factor VIII deficiency, functional platelet disorders, and bleeding secondary from uremia. The mechanism of action of desmopressin involves its binding to the vasopressin V2 receptor located on vascular endothelial cells. This interaction leads to the release of von Willebrand factor, consequently enhancing hemostasis by elevating both von Willebrand factor and factor VIII levels. It has been used in one study for minor procedures such as hydrocele repair or reconstruction the urethra in individuals with minor FXI deficiency. The dose administrated was 0,3 μg/kg for 5 days starting on the day of the surgery and no complications occurred.[7,10,11] Some side effects are headaches, flushing, fluid retention and hyponatremia.

Antifibrinolytic drugs include **TXA** and **epsilon aminocaproic acid**. These lysine analogs bind to the lysine-binding site of plasminogen preventing the binding to fibrin and reducing the risk of postpartum hemorrhage.[7] Side effects are not so usual, some of the most common are abdominal or stomach pain, chills or fever, headache.

The administration of **recombinant factor VIIa** has been used in major surgical procedures in patients with severe FXI deficiency, who already have inhibitors for FXI or patients who are at high risk of developing them.[6]

Another therapy option is the usage of **plasma-derived FXI concentrate**. It is known under the name of Hemoleven, contains AT, heparin and C1 esterase inhibitor and was developed in France and available there since 1992. Thrombotic events are a risk in some patients receiving this treatment, especially those with preexisting risk factors such as older age, peripheral or central vascular disease, morbid obesity. There's been studies that show people developing pulmonary embolism and transient ischemic attacks after the treatment with Hemoleven. The ratio between risk and benefit is still questionable.[12,13]

Pregnancy and FXI deficiency

Pregnant individuals with factor XI deficiency are also at risk of bleeding complications during childbirth. However, this scenario is influenced by the hypercoagulable state that typically accompanies pregnancy, leading to elevated levels of factors V, VII, VIII, IX, and X. In contrast, there is no consistent alteration in factor XI levels during pregnancy. While one study indicated an increase in factor XI levels, other researchers have reported a mild decrease in these levels. Other studies show no correlation between the severity of bleeding during childbirth and the levels of FXI in blood. The best predictor was the outcome during a previous pregnancy and prophylaxis was not mandatory for vaginal delivery.[14,15]

Menorrhagia in FXI deficiency

The hemostatic system plays a pivotal role in regulating both the quantity and duration of menstrual bleeding. Consequently, women who have inherited bleeding disorders often experience

abnormally prolonged or heavy menstrual bleeding. It's worth noting that irregular, premenarchal, or postmenopausal uterine bleeding is atypical in individuals with inherited or acquired hemorrhagic disorders. Instead, common manifestations in these individuals include severe acute bleeding and heavy menstrual bleeding at the time of menarche and persistent, chronic menorrhagia throughout their reproductive years. A comprehensive, multidisciplinary approach is essential for the diagnosis and treatment of individuals with bleeding disorders and associated menorrhagia. Treatment options for menorrhagia in these cases are generally in line with those used for menorrhagia in the general population, with some additional considerations, including desmopressin and replacement therapy, while non-steroidal anti-inflammatory drugs should be avoided. The choice of treatment should take into account various factors, including the patient's preferences, age, and the severity of bleeding. Iron supplementation is very important to address potential iron-deficiency anemia. Initial remedies commonly used for menorrhagia, such as tranexamic acid, combined oral contraceptives, and the levonorgestrel intrauterine system, are typically attempted first. In cases of treatment failure or contraindications, before considering surgical options, treatment with desmopressin is often the preferred choice, especially in patients known to be responsive to it. The availability of desmopressin preparations for self-administration has made home treatment a viable option in carefully selected cases. This form of treatment has proven to be effective and safe when patients are educated to self-administer the medication exclusively during the first two or three heaviest days of their menstrual period. This self-administration should be limited to a maximum of three to four doses, with no more than two consecutive administrations at a 12-hour interval.[16]

Conclusion

In conclusion, factor XI deficiency is a rare autosomal recessive bleeding disorder, most prevalent among Ashkenazi Jews. Spontaneous bleeding episodes are infrequent, and the risk of postoperative bleeding varies widely and doesn't consistently correlate with factor XI activity levels. This discrepancy is particularly evident in gynecological patients.

Prophylactic treatment options are determined based on the extent of surgical invasiveness and may include fresh frozen plasma (FFP), antifibrinolytics, desmopressin, and recombinant factor VIIa. The choice of prophylaxis depends on the specific surgical situation and the patient's individual needs.

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