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REVIEW

Catridecacog: a breakthrough in the treatment of congenital factor XIII A-subunit deficiency?

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Abstract: Circulating factor XIII (FXIII) consists of two active (A) and two carrier (B) subunits in tetrameric form. Congenital FXIII deficiency is a rare autosomal-recessive trait that mostly results from an FXIII A-subunit deficiency. Classic coagulation assays, such as prothrombin time or activated partial thromboplastin time, are not sensitive to FXIII; therefore, specific FXIII assays are necessary to detect the deficiency. The clinical picture of congenital FXIII deficiency comprises abortions, umbilical cord bleeding, increased surgical bleeding, intracerebral hemorrhage (which can, unfortunately, be the very first sign of severe FXIII deficiency), menorrhagia, and wound-healing disorders. Given the risk of intracranial hemorrhage, continued prophylaxis is to be recommended in severe deficiency, even in the actual absence of bleeding symptoms. Functional FXIII half-life decreases in consumptive processes (eg, surgery), explaining why increased dosing is needed in such situations. A recombinant FXIII (rFXIII) subunit-A molecule, which is expressed in *Saccharomyces cerevisiae*, has been evaluated for replacement therapy in congenital FXIII deficiency. The bleeding frequency under continued rFXIII prophylaxis during a year-long treatment period was significantly lower compared to on-demand treatment. Importantly, no severe spontaneous bleedings occurred, and bleeding requiring additional intervention only occurred after relevant trauma. Treatment with rFXIII proved to be safe: antibodies against rFXIII detected in four patients were not considered clinically relevant. No allergic reactions were observed. These data show that rFXIII can be used safely and effectively for continued prophylaxis in congenital FXIII deficiency; it is conceivable that this also holds true for treatment of acute bleeding, but clinical proof of this is pending.

Keywords: FXIII, transglutaminase, bleeding, clot firmness

Introduction

Hemostasis represents a tightly regulated system of various pathways to ensure an optimal equilibrium between excessive bleeding and thrombosis. A clot formed in the presence of calcium ions is usually resistant to proteolytic breakdown, suggesting the presence of an "insoluble" clot. It was noticed early on by Lorand[1] that a single factor (initially called "fibrin-stabilizing factor") is the main one responsible for the mechanical characteristics of insoluble fibrin clots. In 1960, Duckert et al described the first case of a previously unknown congenital hemorrhagic diathesis, which was due to the deficiency of this fibrin-stabilizing factor, or factor XIII (FXIII);[2] the main biochemical abnormality observed at the time was the solubility of the clot in 5 M urea, and it was not until recently that this case was genetically characterized.[3]

Congenital FXIII deficiency is an autosomal-recessive disease,[4] with an estimated prevalence of approximately one in four million worldwide, but with likely clustering.

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Only a few more than 300 cases have been reported, predominantly in Japan.[5] Congenital FXIII deficiency seems, expectedly, more frequent in families with consanguineous marriages, eg, in South Asia.[6] In Pakistan, 80% of the cases detected in a case series over a 10-year period occurred in families with consanguineous marriages.[7]

The clinical significance of FXIII in the maintenance of adequate hemostasis can be deducted from hemorrhagic symptoms observed in patients with FXIII deficiency or inhibiting FXIII antibodies.[8,9] The clinical importance of acquired FXIII deficiency with consumptive processes has been recognized more recently.[10,11] Besides hemostasis, FXIII seems also to play important roles in phagocytosis[12] and tissue repair.[13] Furthermore, FXIII is important in maintaining pregnancies,[14,15] as deficiencies are associated with a higher rate of miscarriages.[16] FXIII deficiency has also been shown to be associated with poor wound healing[17–19] and angiogenesis.[20,21] Other important functions of FXIII comprise osteoblast function[22,23] and the support of the innate immune response to bacteria.[24]

Polymorphisms of the FXIII gene lead to changes in clot properties[25] that seem to be clinically relevant; while intracranial hemorrhage seems more prevalent in patients with the FXIII Val34Leu polymorphism,[26] less myocardial infarctions seem to occur.[27,28] This exemplifies that FXIII is apparently situated at the interface between the maintenance of clot integrity and clot breakdown.[29]

Structure–function relationship

Circulating FXIII consists of two identical proenzyme (A_2) and carrier-protein (B_2) subunits. The A subunit contains the active center, the activation peptide, a calcium-binding site, and free sulfhydryl groups. The B subunit acts as a carrier protein to stabilize subunit A; it also binds fibrinogen and assists in regulating FXIII activity.[30,31] The B subunit is found in plasma in its free form as well as a part of the A_2B_2 tetramer. Usually, the A subunit is completely complexed with B subunits; therefore, the A subunit in its inactive state is found in the tetramer only. Factor XIII can be found circulating in association with fibrinogen.[32]

The gene for subunit A is on chromosome 6 (p24–p25), consists of 160 kilobases and has 15 exons. Mutations or defects associated with FXIII deficiency seem to be without a cluster, but are spread out over the FXIII-A gene, and the mutations seem to be associated with the severity of the disease.[33–35] The mutations (more than 100 described) are mostly missense and nonsense mutations; the gene for the B subunit does not seem to be involved in these cases. The subunit-B gene, consisting of 28 kilobases and with 12 exons, is located on chromosome 1 (q31–q32.1).[36–38] Very few mutations that lead to FXIII-B deficiency have been described.[39]

A very frequent FXIII polymorphism (Val34Leu) seems to play no part in severe (congenital) FXIII deficiency but contributes to the wide range of ("normal") distribution of FXIII activity.[40] Synthesis of subunit A occurs in bone marrow cells, monocytes, and macrophages, as well as hepatocytes; subunit B is synthesized in hepatocytes.[41,42] About 50% of the total FXIII activity is present in platelets as A_2 homodimers. This "tissue transglutaminase 2" – being in fact the intracellular form of FXIII – is found as A_2 homodimer in platelets, megakaryocytes, monocytes, macrophages, the liver, placenta, and uterus,[36,42–46] whereas a clinically relevant contribution of monocytes seems questionable.[47] During steady-state situations, FXIII has a long functional half-life of approximately 10 days,[48] but it is likely to be shorter during consumption (eg, bleeding) situations[49] or with subunit-B deficiency.[50]

Upon thrombin generation, fibrinopeptide A is released from the fibrinogen α-chain and fibrinopeptide B from the fibrinogen β-chain. These steps mark the transition to the fibrin monomer molecule. FXIIIa is generated after thrombin-mediated cleavage of an activation peptide;[51] fibrin itself is a cofactor in the activation of FXIII to FXIIIa, accelerating the activation process. The subsequent calcium-dependent dissociation of the B subunit allows the presentation of the active center through conformational changes.[52–54] Fibrin monomers associate spontaneously in a longitudinal and lateral fashion to form (soluble) fibrin strands. Cross-linking by FXIIIa then generates a mechanically stable, insoluble fibrin clot by cross-linking fibrinogen glutamyl and lysine residues through isopeptide bonds.

Apart from its clot-stabilizing properties, FXIII also anchors α2-antiplasmin to the fibrin clot as well as fibrinogen.[55,56] That way, FXIII activity not only ensures cross-linking and thus mechanical stability of the clot, but at the same time it also guarantees a certain fibrinolytic resistance of the clot and the substrate used to build a fibrin clot.

Detecting and categorizing FXIII deficiencies

FXIII deficiency does not influence classic global coagulation tests, such as prothrombin time (PT)/international normalized ratio (INR) or activated partial thromboplastin time (aPTT), to a clinically relevant extent. Therefore, normal INR or aPTT values do not allow the exclusion of FXIII deficiency, and specific methods need to be employed. At present, most

laboratories use a chromogenic assay, which determines the effect of subunit-A activity.[57] This assay seems to be less accurate in the low range when compared to an incorporation assay based on the natural function of FXIII,[58] which is a modification of earlier assays.[59,60] Antigen measurements have for a long time been associated with increased resource use and longer turnaround times, making them most relevant for scientific research and less so for patient management. The determination of the A_2B_2 tetramer is recommended before such further steps as specific subunit determination or mixing assays (if an inhibitor has to be taken into consideration) are undertaken.[18] However, in daily clinical practice, the detection of FXIII (ie, subunit A) activity is most important, and will correlate in the vast majority of the cases with subunit-A concentration. Immunoassays to detect the FXIII-A subunit on autoanalyzers have recently been marketed.

As FXIII measurements become more and more important in acute-care bleeding management, development of assays that allow a very short turnaround time would be of advantage. It was shown that FXIII deficiency significantly influences whole-blood thrombelastographic assays, and proof-of-principle studies suggest that whole-blood aggregometry can be used for the fast and reliable determination of a potential FXIII deficiency.[61]

As mentioned, patients with congenital FXIII deficiency mostly show aberrations in the FXIII-A gene.[34,35,62] While this leads to direct impairment of FXIII activity through either qualitative or quantitative defects of the A subunit, mutations in the FXIII-B gene lead to decreased FXIII-B expression, and thus in turn to increased FXIII-A degradation (of the normal FXIII-A subunit), due to missing protection by the FXIII-B subunit.[50] Therefore, congenital FXIII deficiency is predominately divided into FXIII-A and FXIII-B deficiency, whereas FXIII-A deficiency can theoretically be further subclassified into quantitative (type 1) and qualitative (type 2) defects.

Acquired FXIII deficiency can be frequently detected in patients with preexisting diseases and ongoing, albeit subclinical, coagulation activation, suggesting that consumption is the main origin of these deficiencies. If these patients undergo surgical stress, bleeding symptoms can occur, and FXIII replacement seems beneficial in these cases. In our experience, acquired FXIII deficiency is frequent, and most of the time not related to inhibitors or drug use, but to the perioperative setting.[11,63,64]

The clinical picture

Congenital FXIII deficiency can manifest very early on in life as bleeding from the umbilical stump.[65] Registry data have shown that intracranial hemorrhage (which can, unfortunately, be the very first sign of severe FXIII deficiency; this is often preceded by trauma in children; intracerebral bleeding may recur in up to a third of cases with a correspondingly high risk of mortality), umbilical cord bleeding (up to 3 weeks after birth), and intramuscular and intracutaneous bleeding are the most frequent bleeding types in congenital FXIII deficiency, with intracranial hemorrhage and umbilical stump bleeding being much more frequent in FXIII deficiency than other coagulation-factor deficiencies.[66] Umbilical bleeding due to FXIII deficiency might be life-threatening in neonates, which is why aggressive diagnostics and replacement therapy are necessary once FXIII deficiency is considered or recognized. Other clinical signs associated with FXIII deficiency[6,7,17,67–70] include spontaneous abortions in early pregnancy; a general bleeding tendency, especially with trauma (this bleeding may be immediate, delayed or repeated); menorrhagia; and wound-healing disorders, which are a common finding.

Peri- and postoperative bleeding is another frequent bleeding type in congenital FXIII deficiency; however, acquired FXIII deficiency is a frequent finding in the perioperative setting, and might contribute – alone or in combination with a preexisting congenital deficiency – to a bleeding diathesis in this setting.[10,11,63,64] In patients with congenital FXIII deficiency, it seems that low levels of FXIII (in the single-figure percentage range) are sufficient to provide clinically adequate hemostasis[71] in a steady-state setting. Retrospective as well as prospective data suggest that we need to differentiate between a congenital and a congenital-plus-acquired deficiency with regard to clinical management. In the acquired-deficiency setting, clinical symptoms seem much more pronounced (ie, occurring at much-higher factor levels) compared to the congenital deficiency setting.[10,11,72–75]

Treatment options for congenital FXIII deficiency

Congenital, symptomatic FXIII deficiency is overall an infrequent finding; as mentioned earlier, the clinical picture is somewhat variable, depending on the severity of the deficiency.[66,76] Long-term replacement therapy for (severe) congenital FXIII deficiency needs always to be considered because of the high risk of central nervous system hemorrhage. As the half-life of FXIII is long in a steady-state situation, replacement is often only needed every 4 weeks,[77] but the frequency of replacement should be adapted to the clinical need; in steady-state situations, 10–20 IU should be given per kilogram of body weight every 4 weeks.

Theoretically, such doses can be given through the application of fresh frozen plasma; however, the volume needed (approximately 20 mL/kg) and the logistics of a frozen material compared to a lyophilized substance make lyophilized factor concentrates the ideal solution for replacement therapy. Various studies showed prophylactic treatment with a plasma-derived product to be effective without relevant toxicity.[78–80] Similar observations with a stringent evaluation protocol have recently been made for recombinant FXIII (catridecacog) in volunteers,[81] as well as patients.[26,82,83] Patients with FXIII below 1% should receive immediate prophylaxis, even if no bleeding complications have occurred.[80] For patients with levels of 1%–4%, primary prophylaxis should also be considered, as there is still a high chance of severe bleeding complications. With FXIII levels >5%, it is generally assumed that no spontaneous severe bleeding will occur, given that FXIII levels of 3%–10% of the normal population mean are sufficient to prevent spontaneous bleeds.[84] However, bleeding might still occur[65] and might be significant (eg, if surgical stress is applied); therefore, higher-than-prophylactic levels are recommended in FXIII-deficient patients undergoing surgery.[63,85] In pregnancy, more frequent replacements with lower doses have been reported to be successful,[69] which is important, as pregnant women with severe congenital FXIII deficiency have a roughly 50% chance of experiencing recurrent pregnancy losses or spontaneous abortions.[86,87] Special caution needs to be taken to secure adequate plasma levels during labor in order to prevent hemorrhagic complications.[69]

In acute bleeding episodes, FXIII replacement should be sufficiently dosed (eg, at 30 IU/kg)[10] to reach 60% activity levels, and with severe or intracranial bleeding, continued monitoring of FXIII levels is mandatory to guarantee sufficient replacement (as half-life is dramatically shortened with situations where consumption is going on). Unlike the purified plasma product, which is essentially the purified A_2B_2 tetramer, the recently introduced recombinant FXIII-A_2 (rFXIII-A_2, catridecacog)[26] combines with free endogenous FXIII-B in plasma to form a functional tetramer. Therefore, patients with a congenital deficiency of the B unit can be expected to have a shortened functional half-life after application of the rFXIII; it is conceivable that rFXIII-A_2 will be functional in B-subunit deficiency, but this awaits clinical confirmation, and until then it remains an off-label indication. Catridecacog was shown to be effective and safe in patients with congenital FXIII deficiency undergoing prophylactic replacement therapy.[26,82,83] While low-titer antibodies against the recombinant protein were detected in some patients, there was no evidence that they were of any clinical relevance.[82] Both the efficacy and the safety profile in pediatric patients were also found to be good.[83] Mean half-life of the new drug under steady-state conditions was found to be approximately 9–15 days.[26,83] In surgical patients, the use of recombinant FXIII (catridecacog) on top of normal FXIII values was not associated with any safety issues, providing additional proof of the safety of such a treatment approach.[88]

Conclusion

Congenital FXIII deficiency is rare, with a prevalence of approximately one in four million. This autosomal-recessive disorder appears to be underdiagnosed, as it is not recognized by classic global tests, such as aPTT or PT. Specific assays need to be implemented and performed to detect the deficiency; early recognition is essential to allow adequate prophylactic therapy, which might save patients from life-threatening bleeding and the potentially related morbidity and mortality. Currently, standard therapy for prophylaxis is performed using plasmatic FXIII concentrate. However, recombinant FXIII (catridecacog) is now commercially available, and has proven to be safe and effective in bleeding prophylaxis with congenital FXIII deficiency. Replacing plasmatic concentrates with recombinant products will render this replacement therapy independent of the need for blood donations. As acquired FXIII deficiency with bleeding complications is very frequent in the peri-interventional setting, further studies will need to evaluate whether the recombinant product can replace the plasmatic concentrate in the noncongenital deficiency setting too. This will ultimately decide whether catridecacog is a breakthrough in FXIII-replacement therapy.

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