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Factor XIII deficiency: a review of literature

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Abstract

Coagulation factor XIII gene, protein structure and function Coagulation factor XIII (FXIII) is a tetrameric (FXIII-A2B2) pro-transglutaminase enzyme with an essential role in the final stage of coagulation cascade by cross linking the fibrin monomers and stabilizing the fibrin clot. Congenital FXIII deficiency is a rare bleeding disorder, with an autosomal recessive trait inheritance, and a frequency of about 1 in 2 million people. Most cases of FXIII deficiency are associated with FXIII-A subunit deficiency and only few FXIII-B subunit deficiencies have been reported. Severe FXIII-A deficiencies are associated with some moderate to severe clinical complications including umbilical bleeding during infancy, impaired wound healing, pregnancy loss in affected women, life-threatening intracranial bleeding and also subcutaneous and soft tissue bleeding. Diagnosis of FXIII deficiency can be achieved by clot solubility tests in 5 M urea or 1% monochloracetic acid as a screening assay, and also quantitative evaluation of the activity or antigenic levels of FXIII A and B subunits. There have been recommendations for primary prophylaxis or replacement therapy in FXIII deficient patients, in order to prevent spontaneous bleeding, bleeding during minor and major surgeries, or prevention of pregnancy loss in women. Acquired FXIII deficiency has also been reported as a result of decreased production or high consumption of FXIII as well as the secretion of autoantibodies against FXIII subunits.

Keywords: FXIII deficiency, bleeding disorders, wound healing, pregnancy, prophylaxis, replacement therapy

Introduction

Coagulation factor XIII gene, protein structure and function

Coagulation factor XIII (FXIII) is a pro-transglutaminase enzyme that circulates in plasma as a two potentially active A subunits (FXIII-A) and two inhibitor/carrier B subunits (FXIII-B). [1, 2] The A subunit which carries the catalytic part of the enzyme is a non-glycosylated single polypeptide chain molecule with 731 amino acid and a molecular mass of 83 kDa, and is synthesized in cells with bone marrow origin.[3-5] The gene coding for A subunit is located on chromosome 6p24-25. It spans 160 kb and consists of 15 exons separated by 14 introns. The A subunit consists of five domains: an activation peptide (residues 1-37), a β-sandwich (residues 38-183), a catalytic core region (residues 184-515) and two β-barrels (barrel 1, residues 516-627 and barrel2, residues 628-731.[6,7] FXIII-B which is produced by hepatocytes is a mosaic protein which consists of ten short consensus repeats, also known as sushi-domain repeats or GP-I structures.[3,8,9] FXIII-B is a single peptide with 641 amino acid, (each sushi-domain consists of about 60 amino acids) and a total molecular mass of approximately 80 kDa.[3] The gene coding for B subunit is located on chromosome 1q31-32. It spans 28 kb and consists of 12 exons and 11 introns. [10,11] FXIII-A present in the plasma is in complexed form in normal conditions, while FXIII-B is in excess and about 50% of it circulates as free un-complexed protein.[1] Unlike plasma FXIII that present as a tetrameric structure (A2B2) the cellular form of FXIII present in platelets, monocytes and tissue macrophages is a homodimer of FXIII-A.[12]

Activated plasma FXIII has an essential role in the final stage of coagulation cascade and the stabilization of fibrin clot. FXIII is activated by thrombin and Ca^{2+} in several process steps. First the cleavage of the FXIII peptide happens by hydrolyzing the Arg37-Gly38 peptide bond in the FXIII-A

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subunit, and then the inhibitory FXIII-B subunits become dissociated in the presence of Ca^{2+}. The cleaved FXIII-A subunit acts as an active form of peptide (FXIIIa or FXIII-A2*). The activation process is accelerated in the presence of fibrin.[13-16] Activated FXIII is a transglutaminase which catalyzes an acyl transfer reaction. FXIIIa cross-links peptide-bound glutamine and lysine residues through isopeptide bonds that covalently cross-links fibrin through an ε(γ-glutamyl) lysine link.[17, 18] Formation of fibrin γ-chain dimers, cross-linking in fibrin α-chains into high molecular weight polymers, and attaching the α2 plasmin inhibitor to fibrin α-chains are the main hemostatic functions of FXIIIa. This functions lead to mechanically stabilizing the fibrin clot and also protects it from shear stresses and the prompt elimination by the fibrinolytic system.[1,18,19] Figure 1 shows the schematic role of FXIII in coagulation cascade. Beside the essential role of FXIII in the coagulation system, it is clinically essential in wound healing, angiogenesis and maintaining the pregnancy. [1,20-23)]

Congenital FXIII deficiency and clinical complications

Congenital FXIII deficiency is a rare bleeding disorder with a frequency of 1/2000000 in general population. [23] The disease is transmitted as an autosomal recessive trait and is more common in countries with high rate of consanguineous marriages. [1, 24] The first patient was described by Duckert et al. in 1960 as a Swiss boy with inherited bleeding diathesis and abnormal clot solubility test in 5 M urea. [25] Congenital FXIII deficiency can be caused by a defect in FXIII-B (formerly known as type I deficiency), a defect in FXIII-A (formerly known as type II deficiency), and probably combined deficiency of FXIII-A and B subunits.[26] FXIII-A deficiency contains quantitative type I deficiency resulting from decreased synthesis of the protein and qualitative type II deficiency resulting from normal or slightly decreased concentration of FXIII-A subunit but functionally defective protein.[27]

FXIII-B deficiency is uncommon and most causes of FXIII deficiency are the result of FXIII-A deficiency. Patients with homozygous FXIII deficiency have severe life-long and sometimes life-treading bleeding complications.

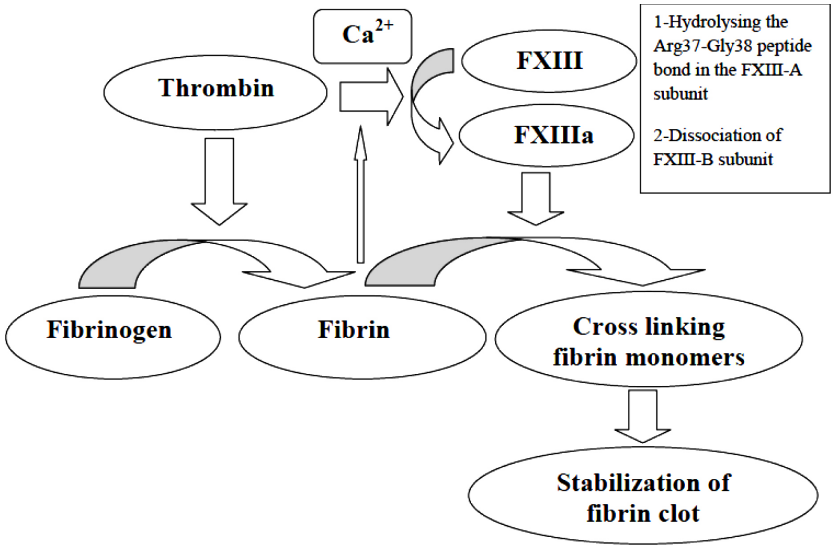
Umbilical bleeding:

Umbilical bleeding is reported in about 80% of cases and it is a characteristic and diagnostic symptom of FXIII deficiency. Bleeding from umbilical stump occurs a few days after birth, when the cord had separated, and can be serious and life-threatening in homozygous FXIII deficiency. It is also to be noted that circumcision of these babies after birth has resulted in severe bleeding. [1,28,29]

Intracranial bleeding:

The incidence of intracranial bleeding in FXIII deficiency is about 30% of reported cases, which is higher than in any other congenital bleeding disorder. The major threat to life in FXIII deficient patients is intracranial bleeding which is reported in 80% of FXIII deficient patients who die due to bleeding.[1,30]

Figure 1. Schematic role of FXIII in coagulation cascade



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Subcutaneous and soft tissue bleeding:

FXIII deficient patients have a life-long tendency for subcutaneous bleeding that characteristically occurs after bruises and trauma. Mouth and gums bleeding is recurrent and a serious common problem during dental procedures which occurs in about 30% of cases. Muscles and joints bleeding can occur without obvious trauma, after minor trauma, or after strenuous exercises. Bleeding into muscles and joints occurs with relatively high frequency, joint bleeding is more commonly peri-articular than intra-articular.[1,30,31]

Other bleeding diathesis:

There are infrequent reports on some other rare bleeding disorders in FXIII deficient patients especially mucous membranous bleeding including epistaxis, renal, gastrointestinal, genital, ear and pleural bleeding. FXIII deficient patients are also at higher risk of bleeding after trauma or surgery. Severe bleeding complications have been reported after abdominal, gynecological, plastic, urological and neurological surgery due to FXIII deficiency.[1,32]

***Delayed wound healing*:**

Delayed wound healing has been reported among 14-29% of patients first recognized with FXIII. Cross-linking of fibrin and fibronectin at the site of injury, the proangiogenic effect and the enhancement of the migration and proliferation of monocytes and fibroblasts are some contributing factors of FXIII in the process of tissue repair and wound healing.[1]

Recurrent abortion and pregnancy loss:

Recurrent abortion and pregnancy loss is a common complication among women suffering from FXIII deficiency. Although FXIII is not required for ovulation, fertilization and implantation of the fertilized egg; it is essential for proper anchoring of the cytotrophoblasts after they invade the endometrium. So, poorly performed cytotrophoblastic and Nitabuch layers leading to increased likelihood of placental detachment and subsequent miscarriage are common in FXIII deficient women.[33-35]

FXIII-A and B gene mutations and Phenotype-Genotype Correlation

Mutations are found in both FXIII-A and FXIII-B genes. Different databases have listed these gene mutations including f13 database (www.f13-database.de), Pubmed (www.ncbi.nlm.nih.gov/pubmed) and the Human Gene Mutation Database (www.hgmd.cf.ac.uk). Based on these databases about 133 different mutations have been reported in FXIII gene where most of them (114 mutations) have been found in FXIII-A and only 19 mutations in FXIII-B gene. Most of these mutations are missense mutations and no mutational hotspots were found in FXIII gene. Deletions/insertions, nonsense and splice site mutations are other mutations reported for the FXIII-A gene.[1, 2] Arg77His and Trp187Arg are the most frequent mutations among Iranian FXIII deficient patients.[36] Table 1 shows the common mutations found in FXIII-A gene.[2] There is no exact genotype and clinical phenotype correlation in FXIII deficiency. Clinical symptoms in patients are different from one patient to the other patient and are usually unpredictable.[1] It is reported that Val34Leu polymorphism in FXIII deficiency is associated with increased FXIII level and activity and this polymorphism leads to moderate protection against coronary artery disease and venous thromboembolism, but is not associated with ischemic stroke.[12, 15, 37]

Laboratory diagnosis of FXIII deficiency

Routine coagulation laboratory tests including prothrombin time, partial thromboplastin time, bleeding time, thrombin time and platelet counts are in normal range in FXIII deficiency and cannot help in diagnosis. The earlier and the most common screening test for FXIII deficiency was based on solubility of fibrin clot in a solution of 2% acetic acid (or1% monochloracetic acid) or 5 M urea. This solubility test is a qualitative test and is positive only if FXIII activity in the patient's plasma is very low, usually below 5% in 5 M urea and below 10% in 2% acetic acid.[38, 39] The exact diagnosis of FXIII level and activity can be performed by quantitative assays. Photometric assays based on 1) ammonia released in Berichrom FXIII kit (Dade Behring, Marburg, Germany) and REA-chrom kit (Reanal, Budapest, Hungary) 2) amine incorporation assay to measure amines covalently cross-linked to a protein substrate in the Pefakit FXIII kit (Pentapharm, Basel, Switzerland) and fluorometric assay developed by N-zyme BioTec kit (Darmstadt, Germany) are quantitative assays for detection of FXIII deficiency.[18] Commercially available ELISA kits have been developed for determination of FXIII-A and B antigenic levels and antibody against FXIII

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Table 1. Common mutations found in FXIII-A gene

Type of Mutations and Region	Beta sandwich	Core	Beta barrel 1	Beta barrel 2	Activated peptid
Missense	Asn60Lys,Arg77Cys Arg77His,Arg78Cys Met159Arg,Tyr167Cys	Pro186Leu,Trp187Arg,Gly210Arg, Gly215Arg,Leu235Arg,Met242Arg Arg252Ile,Arg260Cys,Arg260His, Arg260Leu,Gly262Glu,Ser263Phe Trp283Cys,Pro289Arg,Ser295Arg, Val316Phe,Ala318Val,Arg326Gln Leu354Pro,Ala378Pro,Arg382Ser, Ala394Val,Thr398Asn,Arg408Gln Ser 413Trp,Val414Phe,Gly420Ser, Leu498Pro,Gly501Arg	Arg540Gln Asn541Lys Gly562Arg	Gly592Ser, Arg611His Leu660Pro, Leu667Pro Asp668Gly, Arg703Trp Ser708Asn, His716Arg	
Non sense	c.210T>G, c.514C>T c.523 C>T	c.979C>T, c.1201C>T, c.1171G>T c.1326C>A	-	c.1984C>T, c.1994G>A c.2075G>A	
Insertions/deletions	(–7 to –20)insTT c.291–296insTCGTCC c.249–261del13bp c.397insG c.499–512del14bp	c.599–600delAA, c.689delA, Exon 5 del, ins T866, c.709delG c.869insC, c.1030–1032delAAT, c.1201insC, 127067del33 c.1392–1395delAATT, c.1405–1408delCAAA, Gross Deletion(>100 kb)	c.1652del10bp	c.2002–2003delCT c.2066del C, Exon 15 del	33bpdel c.27delT
Splice site	c.131–132delAG c.319GNT, IVS3+6 T>C IVS3+5 G>A	IVS5–1 G>A, IVS7+1 G>A, c.1111T>G, IVS10+1G, c.2045G>A			
Most common Polymorphisms	Val34Leu, Tyr204Phe, Pro564Leu, Val650Ile, Glu651Gln,				

subunits. Normal range of plasma EXIII activity is between 53.2%-221.3% (mean 105% ± 28.56%)[18] and a plasma FXIII activity of 5%-30% is sufficient for normal plasma coagulation activity. Genetic analyses for detection of causative genetic variants can also be performed.

Treatment and prophylaxis in FXIII deficiency

Treatment strategy:

Although fresh frozen plasma (FFP) and cryoprecipitate (cryo) are good sources of FXIII (1 and 3 unit/mL of coagulation FXIII respectively), and can be used successfully to treatt FXIII deficiency. Because of the risk of transmission of blood born viruses and also availability of pasteurized FXIII concentrates with more safety and higher titer of FXIII (about 240 units/vial), nowadays FFP and cryo are not recommended for treatment of FXIII deficiency, in places which concentrates are available.[1,26,40] The first human FXIII concentrate was from placenta origin (Fibrogammin HS®) then was replaced by plasma extracted FXIII concentrates [Fibrogammin P® (CSL Behring, Marburg, Germany) and FXIII-BLP® (Bio-Product Laboratory, Elstree, United Kingdom)], and later on the recombinant FXIII concentrate was also produced (Novo Nordisk, Bagsvaerd, Denmark). In patients with acute bleeding episodes it is recommended that 10–30 IU/kg of FXIII concentrates be administered until the bleeding has stops.

Prophylaxis strategy:

Because of the long half-life of plasma FXIII (11-14 days), and the fact that a factor XIII level of above 3-5% is usually sufficient to prevent spontaneous bleeding, prophylaxis is the management strategy of choice. Life-long prophylactic therapy every 4-6 weeks by 10-20 U/kg FXIII is recommended in patients with severe FXIII deficiency to prevent life-threatening spontaneous bleeding.[41,42] To significantly reduce the occurrence of bleedings a level higher than 10% is needed. [24]

Replacement therapy in surgery:

For major surgery the plasma FXIII should be maintained over 5% until the wound healing is complete. To achieve this administration of 20–30 U/kg FXIII per day is recommended. For minor

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surgeries administration of 10–20 U/kg FXIII per day for 2–3 days is recommended. [24,43]

Replacement therapy in pregnancy:

Because of the risk of abortion and pregnancy loss starting prophylaxis with a source of FXIII during pregnancy is essential and should be started as early as possible (ideally before 5–6 weeks' gestation). [33] Based on previous studies a plasma level of FXIII greater than 10% is essential for a successful pregnancy. To maintain this level of FXIII, administration of 250 IU/week FXIII is recommended until the 22nd week of gestation. From the 23rd week of gestation increasing the dose to 500 IU/week FXIII is recommended. Also at the labor, administration of a booster dose of (1000 IU) to maintain the plasma level of FXIII over 30% is needed.[35,44,45]

Acquired FXIII deficiency

Acquired FXIII deficiency can arise from decreased production or increased consumption of FXIII as well as the production of autoantibodies against FXIII subunits. Some diseases including leukemia, liver disease, Crohn's disease, disseminated intravascular coagulation, ulcerative colitis, inflammatory bowel disease, Henoch-Scho¨nlein purpura, systemic lupus erythematosus, sepsis, pulmonary embolism, stroke and major surgery are reported to be associated with acquired FXIII deficiency.[1, ,18,27,46] In these patients the plasma level of FXIII usually remains over 30% and rarely requires replacement therapy. Autoantibodies against FXIII subunits have been reported in some patients especially in patients with autoimmune disease. These autoantibodies are either neutralizing or non neutralizing types. Neutralizing autoantibodies affect the activation of FXIII or the activity of activated FXIII and non neutralizing autoantibodies reduce FXIII subunits by forming an immune complex with them and then being cleared from plasma by the reticulo-endothelial system (24). Plasmapheresis, immunosuppression with cyclophosphamide, cyclosporine or combinations, anti-CD20, and intravenous gamma globulins are tools which can be used for the elimination of autoantibodies against FXIII subunits.[1]

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