Coagulation factor XIII deficiency

Diagnosis, prevalence and management of inherited and acquired forms

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Keywords

Factor XIII, transglutaminase, heterozygous deficiency, heterotetramer

Summary

The plasma circulating zymogenic coagulation factor XIII (FXIII) is a protransglutaminase, which upon activation by thrombin and calcium cross-links preformed fibrin clots/fibrinolytic inhibitors making them mechanically stable and less susceptible to fibrinolysis. The zymogenic plasma FXIII molecule is a heterotetramer composed of two catalytic FXIII-A and two protective FXIII-B subunits. Factor XIII deficiency resulting from inherited or acquired causes can result in pathological bleeding episodes. A diverse spectrum of mutations have been reported in the *F13A1* and *F13B* genes which cause inherited severe FXIII deficiency. The inherited severe FXIII deficiency, which is a rare coagulation disorder with a prevalence of 1 in 4 million has been the prime focus of clinical and genetic investigations owing to the severity of the bleeding phenotype associated with it. Recently however, with a growing understanding into the pleiotropic roles of FXIII, the fairly frequent milder form of FXIII deficiency caused by heterozygous mutations has become one of the subjects of investigative research. The acquired form of FXIII deficiency is usually caused by generation of autoantibodies or hyperconsumption in other disease states such as disseminated intravascular coagulation.

Here, we update the knowledge about the pathophysiology of factor XIII deficiency and its therapeutic options.

Schlüsselwörter

Blutgerinnungsfaktor XIII, FXIII, Protransglutaminase, heterozygote Mutationen

Zusammenfassung

Der plasmatische Blutgerinnungsfaktor XIII (FXIII) ist eine Protransglutaminase, die nach Aktivierung durch Thrombin und Kalzium nicht kovalent vernetzte Fibrindimere verknüpft und zusätzlich durch Einfügen von Fibrinolyse-Inhibitoren dem Blutgerinnsel eine bessere mechanische Stabilität sowie Schutz vor vorzeitiger Fibrinolyse verleiht. Plasma -FXIII ist ein Heterotetramer aus 2 katalytischen FXIII-A- und 2 schützenden FXIII-B-Untereinheiten. Ein angeborener oder erworbener Faktor-XIII-Mangel kann zu Blutungskomplikationen führen. Für einen schweren angeborenen FXIII-Mangel konnte ein breites Mutationspektrum im *F13A1*- und *F13B*-Gen ermittelt werden. Trotz der Seltenheit (Prävalenz: 1 in 4 Millionen) stand er vererbbare FXIII-Mangel wegen des Schweregrades an Blutungserscheinungen im Fokus klinischer und genetischer Studien. Mit steigendem Verständnis der pleiotrophen Rolle von FXIII gewinnt der mildere, durch heterozygote Mutationen verursachte FXIII-Mangel zunehmend an Bedeutung in der Forschung. Der erworbene FXIII-Mangel entsteht häufig durch Autoantikörper oder tritt aufgrund der Verbrauchskoagulation bei anderen Grunderkrankungen (z. B. disseminierte intravasale Koagulopathie) auf.

Diese Übersicht soll aktuelles Wissen zur Pathophysiologie des Faktor-XIII-Mangels und den therapeutischen Optionen vermitteln.

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The coagulation factor XIII

Factor XIII (FXIII) is a coagulation factor acting at the end of the coagulation cascade to stabilize preformed fibrin clots. Enzymatically, it is a protransglutaminase. If it is activated to its transglutaminase form FXIIIa (EC 2.3.2.13), it converts loose fibrin polymers into an organized structure by cross-linking the peptide-bound glutamyl and lysine residues of fibrinogen chains through an isopeptide bond, thereby releasing ammonia (1). The cross-linking reaction has a mechanical stabilizing effect on the preformed fibrin clot. In addition, activated FXIII-A cross-links fibrinolytic inhibitors like alpha-2 antiplasmin to fibrin that protects it from fibrinolysis. In the plasma, the zymogenic FXIII circulates in the form of a heterotetramer (FXIII-A2B2) composed of two catalytic A subunits bound to two carrier B subunits. Intracellularly, FXIII is found as a homodimer composed of two A subunits (A2) (2). FXIII-A subunit is mainly synthesized in macrophages, and megakaryocytes (3). Structurally, each A monomeric subunit (4,

5) is composed of an activation peptide (residues 1–37) and four distinct domains: beta-sandwich (residues 38–183), central core (residues 184–515), barrel 1 (residues 516–627) and barrel 2 regions (residues 628–731). The central core domain contains a catalytic triad (common to the transglutaminase family) formed through hydrogen bond interactions between Cys314, His373 and Asp396 (6).

The site of synthesis for FXIII-B subunit has been suggested to be the liver (7). The B subunit is composed of 10 tandem repeats of complement control protein (CCP) modules designated as Sushi domains, which are also observed in proteins of the complement system (8, 9). Gel filtration analysis of ordered deletion constructs of FXIII-B subunit sushi domains produced in vitro in insect *SF9* cell lines have demonstrated that in an in vitro scenario the first Sushi domain is most likely responsible for the binding to FXIII-A and the fourth/ninth Sushi domains participate in the FXIII-B homodimer assembly (10). The B subunit is thought to play a role in stabilization of the A subunit (11, 12).

On activation by thrombin and Ca^{2+} the A and B subunits dissociate. Proteolytic activation by thrombin involves the cleavage of a N-terminal 37-residue peptide called the activation peptide. The cleavage and the calcium binding both serve to induce structural changes that open up the catalytic triad to substrate access (13, 14). This process is accelerated by fibrin because fibrinogen as opposed to fibrin is a poor substrate of activated FXIII-A (15).

As discussed, the clot stabilizing effect of FXIII is achieved by the cross-linking of fibrinogen chains (alpha-alpha, alpha-gamma, gamma-gamma) (15–17) and the cross-linking of antifibrinolytic inhibitors like alpha-2 antiplasmin to FXIII (18, 19). Apart from fibrinogen and alpha-2 antiplasmin, FXIII has many other substrates like fibronectin, vitronectin, collagen, factor V, von Willebrand factor, alpha-2 antiplasmin, actin, myosin, vinculin, thrombospondin, PAI, TAFI 2, AT1 receptor dimers of monocytes. This implicates pleiotropic roles for FXIII in various systems other than the coagulation pathway (20).

The factor XIII genes

The *F13A1* gene maps to the short arm of chromosome 6 (p24–25) and spans >160 kb of genomic DNA consisting of 15 exons encoding a mature protein of 731 amino acids (21, 22).

The *F13B* gene is located on the long arm of chromosome 1 (q32–32.1) and contains 12 exons encoding the mature protein of 641 amino acids (8, 23). Both, *F13A1* and *F13B* genes, are highly polymorphic (24). A number of non synonymous/coding polymorphisms have been reported in the *F13A1* gene (25), the variants Val34Leu in exon 2, Tyr204Phe in exon 5, Pro(CCA)331(CCC)Pro in exon 8, Glu(GAA)567Glu(GAG) and Pro564Leu in exon 12, Val650Ile and Glu651Gln in exon 14.

An association study involving six of the main coding polymorphisms in *F13A1* gene showed that only the Val34Leu is the true functional polymorphism and the rest are in linkage disequilibrium with this polymorphism. In this study only haplotypes containing the "34L" allele showed association with FXIII activation. An even larger number of synonymous/non-coding polymorphisms (>500) are known for the *F13A1* gene and are listed in the factor 13 database (►www.f13-database.de) (26).

Val34Leu polymorphism

The truly functional polymorphism Val34Leu is the most extensively studied. This polymorphism is located 3 residues prior to the thrombin cleavage site and has been shown to accelerate the activation rate by almost 2.5 times in its presence (27). Therefore, the Val34Leu polymorphism is presumed to have a thrombo-protective effect. It was firstly described by Mikkola et al. in 1994 (28) and since then its association has been studied in a large number of prothrombotic conditions like stroke and coronary artery diseases with different and often contradictory findings (29, 30).

Recently, a regulatory polymorphism intron 1 variant IVS1+12(A) was observed to influence the FXIII level using a reporter gene based expression assay (31). Later this polymorphism was found to be highly prevalent in patients with mild factor XIII deficiency (32).

The allelic structure of the B subunit gene is unique in the sense that the 3′ region houses a large number of polymorphisms which may give rise to alternatively spliced isoforms which have differential migration patterns (33, 34). These isoforms individually are the most frequent alleles in populations of European, African and Asian descent, respectively (35). Some other minor alleles with lower frequency have also been described (33, 34). The genetic variation of the *F13B* gene is responsible for some of the population variability in FXIII activity.

Iwata et al. investigated the major phenotypes of FXIII-B by sequencing individuals who had a particular isoform identified by isoelectric focusing (36). One of the isoforms or phenotype was characterized by an A-to-G substitution in exon 3, resulting in the previously described Arg to His amino acid change at codon 95 (37). Functional studies have shown that the Arg variant shows lower affinity for the A subunit (38). Another isoform was characterized by a C-to-G nucleotide change in intron-K (A+144G), a variation previously reported by Ryan et al. (39).

A comprehensive list of coding and non-coding polymorphisms for *F13A* and *F13B* genes can be found on the factor XIII database (►www.f13-database.de).

Inherited severe FXIII deficiency

Since the first description of FXIII-based patient pathology in 1960 by Duckert et al. (40) 112 distinct FXIII mutations have been identified in patents with a broad spectrum of pathological phenotype variability that include post-operative prolonged bleeding and delayed rebleeding, spontaneous abortion during the first trimester of pregnancy due to placenta dysfunction.

Until the 1980s, the research literature consisted of mainly descriptive reports of *F13A1* and *F13B* mutations with associated patient pathological phenotypes that are typically severe and stemming from homozygous mutations. Since then, in addition to the known roles in haemostasis, basic research by a handful of groups worldwide

began to address the broader potential impact of FXIII function on essential, non-haemostatic functions (41), including maintenance of pregnancy, maintaining physiological vascular permeability, cartilage and bone mineralization and calcifying pathophysiologies, and survival after myocardial infarct.

Severe factor XIII deficiency leads to defective cross-linking of fibrin and vulnerability to late re-bleed due to physical instability of the primary haemostatic clot resulting in clinically severe bleeding. Over 500 cases of severe factor XIII deficiency have been reported worldwide. In affected individuals, the first manifestation of bleeding is from umbilical cord after birth, and this occurs in almost two-thirds of cases (26). Other common bleeding symptoms are subcutaneous bleeding, muscle haematoma, haemorrhage after surgery, haemarthrosis, and life threathening intracranial bleeding (34%). Intracranial bleeding is the leading cause of death in severe factor XIII deficiency (42, 26).

The most frequent symptom of mucosal tract is bleeding in the oral cavity (lips, tongue, gum), followed by menorrhagia and epistaxis (42, 26). Intraperitoneal bleeding in women with reproductive age may occur (in 20% of cases) at the time of ovulation (43).

Deficiency of factor XIII results in „delayed bleeding" after trauma. While primary haemostasis in individuals with these traits is normal, the „delayed bleeding" is caused predominantly by premature lysis of haemostatic clots. In addition to a lifelong bleeding tendency, abnormal wound healing (29%) and habitual spontaneous abortion in affected women are common. Wound-healing complications are probably due to fibrinolytic abnormalities and altered vascular permeability and impaired angiogenesis. In recent times patients are diagnosed early and treated appropriately, so the severe bleeding complications associated with the deficiency is rarely seen. A minority of homozygous patients, especially those who have deficient B-subunits, develop bleeding symptoms which only comes to light when they present with a haemorrhagic complication, e.g. after surgery (44).

Clinical manifestation of heterozygous FXIII deficiency

Recently, the heterozygous factor XIII deficiency (FXIII activity approximately 30–60%) that is quite different from the severe inherited factor XIII deficiency in terms of the symptoms has come to the notice of clinicians. Owing to the mild symptoms associated, this form had escaped adequate attention for a long time. Patients with this deficiency normally do not bleed spontaneously. Nevertheless, they may have delayed bleeding upon provocation for example after surgery (e.g. tonsillectomy), dental extraction or any form of physical trauma. Menorrhagia may also be a common symptom especially in those who have in addition mild von Willebrand disease or other heterozygous coagulation factor deficiency or platelet pathology. Furthermore, heterozygous factor XIII deficiency might also result in unsuccessful in vitro fertilization (45).

Careful exploration of the medical history of heterozygous members of affected families earlier done by Egbring did reveal a significant bleeding tendency (46). The first report from the European Thrombosis Research Organization working party (ETRO) concluded that there are heterozygous family members with overlooked symptoms for whom no obvious correlation between measured FXIII activity and clinical presentation was demonstrable (47).

Our group published the conclusions that support further investigation of heterozygous factor XIII deficiency through a broader patient screening approach leading to diagnosis of a significant number of afflicted patients (26, 48, 49). We found a surprisingly large number (40) of heterozygotes for factor XIII deficiency among a population of 200 patients referred to us for genetic analysis, because of a reduced factor XIII activity that in some of the patients was associated with with clinical symptoms. Mutation screening revealed 23 novel missense mutations (16 in *F13A1* and 7 in *F13B* (partly unpublished data). Interestingly, we found a less skewed ratio of *F13A1* and *F13B* gene mutations associated with heterozygous factor XIII deficiency, which was not expected in light of previous reports suggesting that factor XIII deficiency-associated *F13B* gene mutations are rare in comparison with *F13A1* mutations (ratio 1:20).

The heterozygous mutations present a unique phenotypic scenario as one allele alone is causing a mild FXIII deficient phenotype. In the context of the functional heterotetramer this mutation may have a dominant effect, as one mutated allele is affecting statistically 75% of the heterotetramers. The transglutaminase / cross-linking efficiency may be related to the successful maintenance of this heterotetramer as can be seen in FXIII-B deficiencies, which result in the degradation of the partner/catalytic FXIII-A subunit. Therefore, some of these mutations could be affecting the hetero-merization of the FXIII molecule (▶Fig. 1). To underscore the emerging clinical impact of these heterozygous FXIII mutations, we consider some patient statistics from the German population as a model population. Extrapolating from average prevalences of homozygotes and compound heterozygotes – equal to about 1 in 4 millions – the estimated frequency of heterozygotes is 1/1000, implying that up to 80 000 individuals in Germany may bear heterozygous *F13A* or *F13B* mutations. Therefore, there are a number of undiscovered individuals that might potentially benefit from management strategies in the event of bleeding induced by trauma (accident, surgery etc.) if and when the inherited factor XIII heterozygous deficiency is more clearly defined in clinical and molecular aspects.

Classification of inherited FXIII deficiency severity

The recognition of mild factor XIII deficiency as a genuine inherited defect with a definite prevalence in the general population has opened up the possibility of a broader classification for factor XIII deficiency severity. Recently, the "Project on Consensus Definitions in Rare Bleeding Disorders" suggested an associative classification of factor XIII deficiency severity based on measured FXIII activity and clinical bleeding severity (50).

Accordingly, factor XIII deficiency is classified:

- Severe deficiency, undetectable FXIII activity associated with spontaneous major bleeding.
- Moderate deficiency, <30% FXIII activity associated with mild spontaneous or triggered bleeding.
- Mild deficiency, >30% FXIII activity associated with a mostly asymptomatic disease course.

Acquired FXIII deficiency and FXIII inhibitors

Acquired factor XIII deficiency (51) may be due to impaired synthesis of B-subunits in liver (hepatitis, acute liver failure) and/or increased consumption due to leukemia, inflammatory bowel disorder, sepsis, major surgery, trauma, pulmonary embolism, stroke, leukemia, Crohn´s disease, ulcerative colitis, Henoch Schoenlein purpura, liver cirrhosis, sepsis, and disseminated intravascular coagulation.

In these cases, plasma FXIII levels are usually in the range of 30–70%. Whether the low FXIII contributes to haemorrhagic complications in these diseases remains to be proven.

Treatment of patients bleeding from the small bowel in Henoch-Schoenlein purpura and from large bowel in ulcerative colitis with FXIII concentrate has been reported to be effective in controlling the bleeding (52). Apart from these causes development of autoantibodies against FXIII-A (mostly) or FXIII-B (very rare) subunit can also result in acquired factor XIII deficiency (53). Approximately 36 cases have been reported for autoantibody against FXIII A subunit. Some of these antibodies have been characterized in terms of their influence on the activation of FXIII, FXIII activity or binding to fibrin (54–56). Almost a third of these cases had systemic lupus erythematosus (SLE) (57).

The first report of an autoantibody against the B subunit was reported in a Hungarian patient with "acquired" F XIII deficiency due to anti-FXIII-B "autoantibodies" who manifested severe bleeding symptoms (58). More recently a case of alloantibodies against the B subunit of plasma FXIII was reported in a Japanese patient with congenital deficiency (59). It's interesting to note that the Japanese population seems to show a much higher prevalence/detection rate for acquired factor XIII deficiency (60). This could be owing to well-informed nationwide surveys conducted by the Japanese group in this regard (60, 61).

Inhibitor development leading to reduced FXIII activity is a rare event. Inhibitors have been described in congenitally FXIII deficient patients being treated with FXIII concentrate (62). However, most inhibitors (IgG antibodies) arise in patients with no pre-existing Factor XIII deficiency. FXIII inhibitors arise de novo (22 cases worldwide), in the course of other diseases (e.g. systematic lupus erythematosus) and often in relation to chronic therapy with a variety of drugs (e.g. isoniazid, penicillin, phenytoin, ciprofloxacin). Inhibitors may also appear in patients without any obvious chronic disease (63).

There is limited data on therapy of patients bleeding due to acquired FXIII inhibitor. Most treatment strategies focus on the immediate treatment of acute bleeds (63) using cryoprecipitate, fresh frozen plasma, fibrogammin or even recombinant FVIIa.

The direct inhibitor elimination approach is also practiced (64) using immunosuppressives, immunoadsorption, routine plasmapheresis or rituximab (anti-CD20 monoclonal antibody).

Bleedings in these cases may be severe and difficult to treat (64). Several cases have died of cerebral haemorrhage. Almost all of these neutralizing inhibitors have been observed to develop against FXIII-A subunit. Some of these have been characterized for the epitope on the A subunit to which they bind (e.g. calcium binding site) (53). However, as mentioned Ichinose et al. reported an alloantibody against the B subunit in a Japanese FXIII deficient patient receiving FXIII concentrate which had a neutralizing effect and also resisted further FXIII substitution.(59). Neutralizing antibodies are usually detected by mixing assays (mixing patient and control plasma samples and evaluating the measure of correction for FXIII activity). Non-neutralizing antibodies on the other hand can only be detected with specific binding assays.

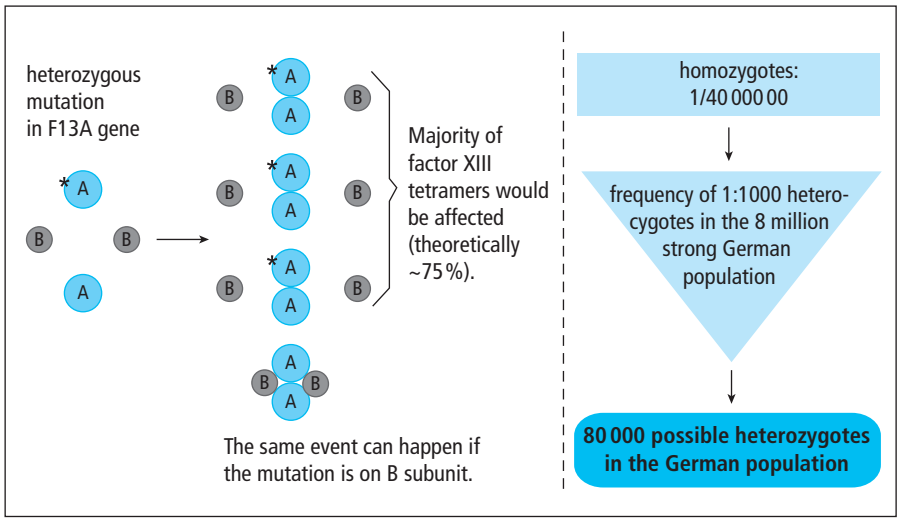

Fig. 1 The heterozygous scenario and its possible clinical and/or pathological implication: The main message is that even a single affected allele has the potential to have an impact on the heteromerization of the FXIII-A2B2 heterotetramer. Theoretically, this could influence almost 75% of the circulating heterotetramers. The pathological impact on the carrier will depend on specific penetrance and expressivity of the variant. It also depends on the risk the patient is exposed to because mild factor XIII deficiency is usually asymptomatic. Symptoms become apparent only in conditions involving trauma (e.g. perioperative conditions). This implies that a large number of heterozygotes might be predisposed to such risks exist in the general population (approx. 80 000 heterozygotes for the 8 millions German inhabitants).

Diagnosis of FXIII deficiency

The standard laboratory clotting tests – prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, platelet counts, bleeding time – are normal, while thromboelastogram (maximum clot firmness) is abnormal. Earlier factor XIII deficiency diagnosis was mainly based on positive clot solubility test (rapid dissolution of clot in 1% monochloracetic acid or 5 mol/l urea). It is a qualitative test and is positive only if FXIII activity in the patient's plasma is zero, or approaching zero (65). If clot solubility in these reagents is found, it is important to perform some simple mixing experiments with normal plasma to make sure that the observed clot solubility is the result of factor XIII deficiency and not due to the presence of a FXIII inhibitor. Reliable diagnostic methods for the determination of plasma FXIII activity and antigen levels have been developed. The factor XIII deficiency diagnosis protocol requires a number of assays, which test for both activity as well as antigen levels. Estimation of FXIII activity using quantitative (e.g. photometric assays which measure the ammonia released during a transglutaminase reaction) or incorporation assays (dansylcadaverine-casein assay which measures the level of incorporation of a labelled amine into a protein substrate) during transglutaminase mediated cross linking. The technical aspects of these assays have been discussed in a recent review (66). The range of plasma FXIII activity within the normal population is very wide, ranging between 60–250% of the standard normal plasma value. The FXIII levels are also influenced by non-genetic variables like age and sex (67). Quantitative assays (e.g. photometric) are quite inaccurate at levels of FXIII activity below 10% of normal therefore in a modification of the earlier photometric assay a blank plasma sample evaluation was added to correct for the FXIII-A-independent NADH consuming and ammonia-producing reactions present in the plasma (68).

The concentrations of the A and B subunits can be determined by immunological techniques like ELISA or western blotting. While antibodies for both A and B subunits as well as a sandwich ELISA for the complete heterotetramer exist commercially, a detection system for detection free B subunit has as yet to be commercialized. Further conformation of the disease can be made by the complete exonic/regulatory region sequencing of the *F13A1* or *F13B* genes to identify causative genetic variants. A publication from the ISTH joint SSC committee has recently suggested an algorithm in which the diagnosis of factor XIII deficiency needs to be approached (69). This involves a preliminary analysis of FXIII activity, followed by antigenic detection (FXIII-A2B2 first, followed by individual subunits in order identify the type of deficiency) and finally ending up with gene screening.

> Also the guidelines redefine the typing of factor XIII deficiency especially inherited FXIII-A deficiency which can be divided into two types:
> - Type 1 shows combined loss of activity as well as antigen.
> - In type 2 antigen (FXIII-A2B2 heterotetramer) is normal to mildly reduced but activity is low (i.e. a dysfunctional protein variant with no loss in antigenic stability).

Mutational heterogeneity in *F13A1* and *F13B* genes

A total of 112 different mutations have been reported so far in the *F13A* and *F13B* genes. As expected (since the A subunit is the catalytic part) a majority of the mutations (96 out of 112) were localized to the *F13A1* gene.(26) Missense mutations were the most common mutation in the *F13A1* subunit gene accounting for ~48% (53 out of 112) of mutations. There are 46 missense, 22 deletions, 10 splice site, 12 nonsense, 6 insertion mutations reported so far for the *F13A1* gene.

Mutations in *F13B* gene were much lower in number. Only 16 different mutations have been reported so far. Splice site mutation in intron 5 (IVS5–1 G>A) seems to be the most common mutation since it was already reported in six unrelated families from UK, Macedonia, Serbia, Kosovo, Czech Republic and the Netherlands (26). If we divide the mutations on the basis of their genetic combination (heterozygous, compound heterozygous and homozygous) we observe that amongst heterozygous mutations, mutations are far more frequent in *F13B* gene than that observed for homozygous mutations (26, 48, 49). Mutations like non-sense, deletion and splice site are causative by their sheer nature; on the other hand missense mutations on their own may or may not be predictive based on their spatial and functional importance in the protein structure. Therefore, clinicians need to look at the all-possible investigation tools including previous reports in literature, expression analysis, in silico data etc. before assigning a missense variant as causative.

Treatment of patients with inherited FXIII deficiency

Whole blood, fresh frozen plasma, stored plasma, plasma derived concentrate and cryoprecipitate have all been used successfully in the treatment of factor XIII deficiency and are adequate sources of FXIII (70). Recently a recombinant FXIII has become available (71). In practice it has been observed that even very low levels of FXIII (>3–10%) in plasma are sufficient for controlling bleeding. This plus the fact that in vivo half-life of FXIII after infusion is long (11–14 days) makes prophylaxis for factor XIII deficiency eminently practicable and manageable. A limited number of randomized crossover studies have reported no pharmacokinetic or tolerability differences between FXIII prepared from human plasma, placenta or recombinant FXIII (72). Recent studies with recombinant FXIII suggest a single 35 IU kg^{-1} rFXIII dose for children as well as adult patients (73, 74). The traditionally used plasma derived pasteurized FXIII concentrate (Fibrogammin) is also suggested at a recommended dosage of 20–30 IU/kg body weight – monthly for mild and moderate levels of bleeding, while in severe bleeding (especially intracranial haemorrhages) the dosage is increased up to 50 IU/kg of body weight and applied at more frequent intervals.

Pregnant women with severe factor XIII deficiency should receive prophylactic treatment to maintain pregnancy. In addition to prophylactic therapy, affected indi-

viduals who undergo surgery or trauma will require more intensive replacement therapy. In case FXIII concentrates are not available, fresh frozen plasma is given prophylactically in doses of 2–3 ml/kg body weight every 3–4 weeks. Cryoprecipitate can be administered in a dose of 1 vial per 10–30 kg of body weight every 3 to 4 weeks. Patients with heterozygous (mild) factor XIII deficiency (activity 30–70%) do not bleed spontaneously. Substitution with FXIII concentrate (10–20 IU/kg body weight) is recommended in patients with bleeding history due to pregnancy (postpartum bleeding), neurosurgery, and abdominal surgery. Antifibrinolytics (e.g. tranexamic acid, 3 g daily) is also useful in the treatment and prevention of bleeding as an additional treatment (75).

One limitation of the recombinant FXIII over plasma derived FXIII is that it does not contain the B subunit and is most likely going to be ineffective for patients with B subunit deficiencies.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Lorand L, Losowsky MS, Miloszewski KJ. Human factor XIII: fibrin-stabilizing factor. Prog Hemost Thromb 1980; 5: 245–290.
2. Schwartz ML, Pizzo SV, Hill RL, McKee PA. Human Factor XIII from plasma and platelets. Molecular weights, subunit structures, proteolytic activation, and cross-linking of fibrinogen and fibrin. J Biol Chem 1973; 248: 1395–1407.
3. Muszbek L, Ariens RA, Ichinose A, Isth Ssc Subcommittee On Factor X. Factor XIII: recommended terms and abbreviations. J Thromb Haemost 2007; 5: 181–183.
4. Weiss MS, Metzner HJ, Hilgenfeld R. Two nonproline cis peptide bonds may be important for factor XIII function. FEBS Lett 1998; 423: 291–296.
5. Yee VC, Pedersen LC, Le Trong I et al. Three-dimensional structure of a transglutaminase: human blood coagulation factor XIII. Proc Natl Acad Sci USA 1994; 91: 7296–7300.
6. Yee VC, Le Trong I, Bishop PD et al. Structure and function studies of factor XIIIa by x-ray crystallography. Semin Thromb Hemost 1996; 22: 377–384.
7. Kloczko J, Wereszczynska U, Wojtukiewicz M et al. Fibrin stabilization, factor XIII transamidase activity and subunits "A" and "B" concentration in plasma of patients with liver cirrhosis. Folia Haematol Int Mag Klin Morphol Blutforsch 1986; 113: 539–544.
8. Bottenus RE, Ichinose A, Davie EW. Nucleotide sequence of the gene for the b subunit of human factor XIII. Biochemistry 1990; 29: 11195–11209.
9. Ichinose A, McMullen BA, Fujikawa K, Davie EW. Amino acid sequence of the b subunit of human factor XIII, a protein composed of ten repetitive segments. Biochemistry 1986; 25: 4633–4638.
10. Souri M, Kaetsu H, Ichinose A. Sushi domains in the B subunit of factor XIII responsible for oligomer assembly. Biochemistry 2008; 47: 8656–8664.
11. Souri M, Koseki-Kuno S, Takeda N et al. Administration of factor XIII B subunit increased plasma factor XIII A subunit levels in factor XIII B subunit knock-out mice. Int J Hematol 2008; 87: 60–68.
12. Souri M, Koseki-Kuno S, Takeda N et al. Male-specific cardiac pathologies in mice lacking either the A or B subunit of factor XIII. Thromb Haemost 2008; 99: 401–408.
13. Komaromi I, Bagoly Z, Muszbek L. Factor XIII: novel structural and functional aspects. J Thromb Haemost 2011; 9: 9–20.
14. Kohler HP. Interaction between FXIII and fibrinogen. Blood 2013; 121: 1934.
15. Smith KA, Adamson PJ, Pease RJ et al. Interactions between factor XIII and the alphaC region of fibrinogen. Blood 2011; 117: 3460–3468.
16. Smith KA, Pease RJ, Avery CA et al. The activation peptide cleft exposed by thrombin cleavage of FXIII-A(2) contains a recognition site for the fibrinogen alpha chain. Blood 2013; 121: 2117–2126.
17. Doolittle RF, Hong S, Wilcox D. Evolution of the fibrinogen gamma' chain: implications for the binding of factor XIII, thrombin and platelets. J Thromb Haemost 2009; 7: 1431–1433.
18. Fraser SR, Booth NA, Mutch NJ. The antifibrinolytic function of factor XIII is exclusively expressed through alpha(2)-antiplasmin cross-linking. Blood 2011; 117: 6371–6374.
19. Van Giezen JJ, Minkema J, Bouma BN, Jansen JW. Cross-linking of alpha 2-antiplasmin to fibrin is a key factor in regulating blood clot lysis: species differences. Blood Coagul Fibrinolysis 1993; 4: 869–875.
20. Richardson VR, Cordell P, Standeven KF, Carter AM. Substrates of Factor XIII-A: roles in thrombosis and wound healing. Clin Sci (Lond) 2013; 124: 123–137.
21. Ichinose A, Davie EW. Characterization of the gene for the a subunit of human factor XIII (plasma transglutaminase), a blood coagulation factor. Proc Natl Acad Sci USA 1988; 85: 5829–5833.
22. Ichinose A, Davie EW. Primary structure of human coagulation factor XIII. Adv Exp Med Biol 1988; 231: 15–27.
23. Webb GC, Coggan M, Ichinose A, Board PG. Localization of the coagulation factor XIII B subunit gene (F13B) to chromosome bands 1q31–32.1 and restriction fragment length polymorphism at the locus. Hum Genet 1989; 81: 157–160.
24. Anwar R, Gallivan L, Edmonds SD, Markham AF. Genotype/phenotype correlations for coagulation factor XIII: specific normal polymorphisms are associated with high or low factor XIII specific activity. Blood 1999; 93: 897–905.
25. De Lange M, Andrew T, Snieder H et al. Joint linkage and association of six single-nucleotide polymorphisms in the factor XIII-A subunit gene point to V34L as the main functional locus. Arterioscler Thromb Vasc Biol 2006; 26: 1914–1919.
26. Biswas A, Ivaskevicius V, Seitz R et al. An update of the mutation profile of factor 13 A and B genes. Blood Rev 2011; 25: 193–204.
27. Ariens RA, Philippou H, Nagaswami C et al. The factor XIII V34L polymorphism accelerates thrombin activation of factor XIII and affects cross-linked fibrin structure. Blood 2000; 96: 988–995.
28. Mikkola H, Syrjala M, Rasi V et al. Deficiency in the A-subunit of coagulation factor XIII: two novel point mutations demonstrate different effects on transcript levels. Blood 1994; 84: 517–525.
29. Li B, Zhang L, Yin Y et al. Lack of evidence for association between factor XIII-A Val34Leu polymorphism and ischemic stroke: a meta-analysis of 8,800 subjects. Thromb Res 2012; 130: 654–660.
30. Kohler HP, Schroder V. Role of coagulation factor XIII in cardio- and cerebrovascular diseases. Hämostaseologie 2002; 22: 53–58.
31. Wang W, Huang L, Ma Q et al. Homozygous intronic mutation leading to inefficient transcription combined with a novel frameshift mutation in F13A1 gene causes Factor XIII deficiency. J Hum Genet 2011; 56: 460–463.
32. Ivaskevicius V, Biswas A, Thomas A et al. A common F13A1 intron 1 variant IVS1+12(A) is associated with mild Factor XIII deficiency in Caucasian population. Ann Hematol 2013; 92: 975–979.
33. Board PG. Genetic polymorphism of the B subunit of human coagulation factor XIII. Am J Hum Genet 1980; 32: 348–353.
34. Board PG. Genetic heterogeneity of the B subunit of coagulation factor XIII: resolution of type 2. Ann Hum Genet 1984; 48: 223–228.
35. Kamboh MI, Ferrell RE. Genetic studies of low abundance human plasma proteins. II. Population genetics of coagulation factor XIIIB. Am J Hum Genet 1986; 39: 817–825.
36. Iwata H, Kitano T, Umetsu K et al. Distinct C-terminus of the B subunit of factor XIII in a population-associated major phenotype: the first case of complete allele-specific alternative splicing products in the coagulation and fibrinolytic systems. J Thromb Haemost 2009; 7: 1084–1091.
37. Nakamura S, Ohue O, Abe K. Genetic polymorphism of coagulation factor XIII B subunit in the Japanese population: description of three new rare alleles. Hum Genet 1986; 73: 183–185.
38. Komanasin N, Catto AJ, Futers TS et al. A novel polymorphism in the factor XIII B-subunit (His95Arg): relationship to subunit dissociation and venous thrombosis. J Thromb Haemost 2005; 3: 2487–2496.
39. Ryan AW, Hughes DA, Tang K et al. Natural selection and the molecular basis of electrophoretic variation at the coagulation F13B locus. Eur J Hum Genet 2009; 17: 219–227.
40. Duckert F, Jung E, Shmerling DH. A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilizing factor deficiency. Thromb Diath Haemorrh 1960; 5: 179–186.
41. Muszbek L, Bereczky Z, Bagoly Z et al. Factor XIII: a coagulation factor with multiple plasmatic and cellular functions. Physiol Rev 2011; 91: 931–972.
42. Ivaskevicius V, Seitz R, Kohler HP et al. International registry on factor XIII deficiency: a basis

formed mostly on European data. Thromb Haemost 2007; 97: 914–921.
43. Lak M, Peyvandi F, Ali Sharifian A et al. Pattern of symptoms in 93 Iranian patients with severe factor XIII deficiency. J Thromb Haemost 2003; 1: 1852–1853.
44. Miloszewski KJA, Losowsky MS. Fibrin stabilisation and factor XIII deficiency. In: Francis L, ed. Fibrinogen, Fibrin Stabilisation and Fibrinolysis. Chichester: Ellis Horwood, 1988: 175–202.
45. Ivaskevicius V, van der Ven K, van der Ven H et al. Successful in vitro fertilization under FXIII concentrate substitution in female with inherited FXIII-A subunit deficiency. Hämostaseologie 2008; 28: P-02C-06.
46. Seitz R, Duckert F, Lopaciuk S et al. ETRO Working Party on Factor XIII Questionnaire on Congenital Factor XIII Deficiency in Europe: Status and Perspectives. Semin Thromb Hemost 1996; 22: 415–418.
47. Egbring R, Seitz R, Gürten GV et al. Bleeding complications in heterozygotes with congenital Factor XIII deficiency. In: Fibrinogen 3. Biochemistry, biological functions, gene regulation and expression. Mosesson MW et al. (Hrsg). Amsterdam: Elsevier 1988; 341–346.
48. Ivaskevicius V, Biswas A, Bevans C et al. Identification of eight novel coagulation factor XIII subunit A mutations: implied consequences for structure and function. Haematologica 2010; 95: 956–962.
49. Ivaskevicius V, Biswas A, Loreth R et al. Mutations affecting disulphide bonds contribute to a fairly common prevalence of F13B gene defects: results of a genetic study in 14 families with factor XIII B deficiency. Haemophilia 2010; 16: 675–682.
50. Peyvandi F, Di Michele D, Bolton-Maggs PH et al. Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity. J Thromb Haemost 2012; 10: 1938–1943.
51. Ichinose A. Hemorrhagic acquired factor XIII (13) deficiency and acquired hemorrhaphilia 13 revisited. Semin Thromb Hemost 2011; 37: 382–388.
52. Lorenz R, Born P, Classen M. Substitution of factor XIII concentrate in treatment refractory ulcerative colitis. A prospective pilot study. Med Klin (Munich) 1994; 89: 534–537.
53. Luo YY, Zhang GS. Acquired factor XIII inhibitor: clinical features, treatment, fibrin structure and epitope determination. Haemophilia 2011; 17: 393–398.
54. Lorand L. Fibrinoligase: the fibrin-stabilizing factor system of blood plasma. Ann NY Acad Sci 1972; 202: 6–30.
55. Lorand L. Hemorrhagic disorders of fibrin stabilization. In: Ogston D, Bennett B (eds). Hemostasis: Biochemistry, Physiology and Pathology. London: John Wiley & Sons Ltd. 1977; 405–423
56. Fukue H, Anderson K, McPhedran P et al. A unique factor XIII inhibitor to a fibrin-binding site on factor XIIIA. Blood 1992; 79: 65–74.
57. Lorand L, Velasco PT, Hill JM et al. Intracranial hemorrhage in systemic lupus erythematosus associated with an autoantibody against actor XIII. Thromb Haemost 2002; 88: 919–923.
58. Ajzner E, Schlammadinger A, Kerenyi A et al. Severe bleeding complications caused by an autoantibody against the B subunit of plasma factor XIII: a novel form of acquired factor XIII deficiency. Blood 2009; 113: 723–725.
59. Wada H, Souri M, Matsumoto R et al. Alloantibodies against the B subunit of plasma factor XIII developed in its congenital deficiency. Thromb Haemost 2013; 109: 661–668.
60. Ichinose A, Souri M, Japanese collaborative research group on "Acquired haemorrha-philia due to factor Xd. As many as 12 cases with haemorrhagic acquired factor XIII deficiency due to its inhibitors were recently found in Japan. Thromb Haemost 2011; 105: 925–927.
61. Ichinose A, Souri M. Reduced difference of á(2)-plasmin inhibitor levels between plasma and serum in patients with severe factor XIII deficiency, including autoimmune haemorrhaphilia due to anti-factor XIII antibodies. Int J Hematol 2012; 95: 47–50.
62. Franchini M, Frattini F, Crestani S, Bonfanti C. Acquired FXIII inhibitors: a systematic review. J Thromb Thrombolysis 2013; 36: 109–114.
63. Kessel R, Hu C, Shore-Lesserson L et al. A child with acquired factor XIII deficiency: case report and literature review. Haemophilia 2013; 19: 814–826.
64. Miesbach W. Rituximab in the treatment of factor XIII inhibitor possibly caused by Ciprofloxacin. Thromb Haemost 2005; 93: 1001–1003.
65. Anwar R, Miloszewski KJ. Factor XIII deficiency. Br J Haematol 1999; 107: 468–484.
66. Katona E, Penzes K, Molnar E, Muszbek L. Measurement of factor XIII activity in plasma. Clin Chem Lab Med 2012; 50: 119402.
67. Ariens RA, Kohler HP, Mansfield MW, Grant PJ. Subunit antigen and activity levels of blood coagulation factor XIII in healthy individuals. Relation to sex, age, smoking, and hypertension. Arterioscler Thromb Vasc Biol 1999; 19: 2012–2016.
68. Karpati L, Penke B, Katona E et al. A modified, optimized kinetic photometric assay for the determination of blood coagulation factor XIII activity in plasma. Clin Chem 2000; 46: 1946–1955.
69. Kohler HP, Ichinose A, Seitz R, Ariens RA, Muszbek L, Factor X, et al. Diagnosis and classification of factor XIII deficiencies. J Thromb Haemost 2011; 9: 1404–1406.
70. Fadoo Z, Merchant Q, Rehman KA. New developments in the management of congenital factor XIII deficiency. J Blood Med 2013; 4: 65–73.
71. Inbal A, Oldenburg J, Carcao M et al. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. Blood 2012; 119: 5111–5117.
72. Lovejoy AE, Reynolds TC, Visich JE et al. Safety and pharmacokinetics of recombinant factor XIII-A2 administration in patients with congenital factor XIII deficiency. Blood 2006; 108: 57–62.
73. Williams M, Will A, Stenmo C et al. Pharmacokinetics of recombinant factor XIII in young children with congenital factor XIII deficiency and comparison with older patients. Haemophilia 2013; 20: 99–105.
74. Bishop PD, Morton KM. Safety, pharmacokinetics, and immunogenicity of single-doserFXIII administration to healthy volunteers. J Thromb Haemost 2005; 3: 922–928.
75. Dirkmann D, Gorlinger K, Gisbertz C et al. Factor XIII and tranexamic acid but not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. Anesth Analg 2012; 114: 1182–1188.

