Congenital factor XIII deficiency: diagnosis, prevalence and treatment modalities in 2020

Lucia Rugeri, Unité hémostase clinique, hospices civils de Lyon, groupement hospitalier Est, Lyon, France
Séverine Bouttefroy, Unité hémostase clinique, hospices civils de Lyon, groupement hospitalier Est, Lyon, France
Émilie Jousselme, Laboratoire d'hémostase, hospices civils de Lyon, groupement hospitalier Est, Lyon, France
Christophe Nougier, Laboratoire d'hémostase, hospices civils de Lyon, groupement hospitalier Est, Lyon, France
Sandrine Meunier, Unité hémostase clinique, hospices civils de Lyon, groupement hospitalier Est, Lyon, France

Off-prints : L. Rugeri
lucia.rugeri@chu-lyon.fr

Déficit congénital en facteur XIII : quelles actualités sur la prévalence, le diagnostic clinique, biologique et les modalités thérapeutiques en 2020 ?

facteur XIII, hémorragie, diagnostic, traitement

Résumé

Le déficit congénital en facteur XIII (FXIII) représente, en France, 6 % des déficits hémorragiques rares. Le FXIII est une protéine ayant, d'une part, pour effet d'augmenter la résistance du caillot, à la toute fin de la cascade de la coagulation, et ayant d'autre part, un rôle dans le maintien de la grossesse. Les formes sévères sont révélées, dans 80 % des cas, par une hémorragie à la chute du cordon ombilical en période néonatale ou (30 % des cas) par une hémorragie intracrânienne (HIC) spontanée. Le déficit en FXIII n'est pas dépisté par les tests standards (taux de prothrombine et temps de céphaline avec activateur) puisqu'il intervient après la formation initiale du caillot. Il est recommandé, pour son diagnostic, d'utiliser une technique de mesure de l'activité fonctionnelle du FXIII puis une technique antigénique pour déterminer le type de déficit. Des techniques mesurant l'antigène FXIII-A possèdent une excellente corrélation avec la mesure fonctionnelle du FXIII ainsi qu'un seuil de détection très bas (> 4 %). Leur automatisation permet donc le dosage spécifique du FXIII, indiqué devant des signes cliniques évocateurs. En France, le traitement repose sur l'administra-

Abstract

Congenital factor XIII (FXIII) deficiency accounts for 6% of rare bleeding disorders in France. FXIII is a protein with a two-fold role: 1) it increases clot strength at the very end of the coagulation cascade; and 2) contributes towards maintaining pregnancy. Around 80% of severe forms of this disorder are revealed by abnormal bleeding when the umbilical cord becomes detached during the neonatal period, and 30% by spontaneous intracranial haemorrhage (ICH). FXIII deficiency cannot be detected using standard tests - prothrombin time and partial thromboplastin time - since FXIII initially acts following initial clot formation. A FXIII functional activity assay is recommended for diagnosis, and a FXII antigen assay is recommended to classify the FXIII deficiency. FXIII-A antigen assays correlate accurately with functional measures and present a very low detection threshold (less than 4%). Their automation therefore makes it possible to specifically measure FXIII, which is indicated when tell-tale clinical signs are observed. In France, treatment is based on the administration of plasma-derived FXIII concentrates (Fibrogammin®), which have a half-life of between 11 and 14 days. In cases of acute

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tion de concentrés de FXIII d'origine plasmatique (Fibrogammin®) dont la demi-vie est de 11 à 14 jours. En cas d'hémorragie aiguë, en particulier intracérébrale, la dose initiale doit être de 20 à 40 UI/kg. D'ailleurs, devant le risque élevé d'HIC, il est recommandé de débuter un traitement prophylactique dès le diagnostic, dont les doses et le rythme doivent être au minimum de 20-40 UI/kg toutes les quatre semaines.

haemorrhage, in particular intracerebral haemorrhage, the initial dose should be between 20 and 40 IU/kg. Due to the high risk of ICH, the recommendation is to initiate prophylaxis replacement therapy as soon as the diagnosis has been made. The recommended dose and dosing interval are at least 20-40 IU/kg once every four weeks.

Congenital coagulation protein deficiencies are rare disorders. Congenital factor XIII (FXIII) deficiency accounts for 6% of these deficiencies in France and worldwide, with a prevalence of around two cases per million inhabitants [1, 2]. This low prevalence, the absence of screening using standard tests, and the analytical variability of specific tests are obstacles to standardising the diagnosis and therapeutic management of the disorder. The objectives of this review are to describe recent data on the physiological role of FXIII, the prevalence of clinical manifestations, biological screening methods, diagnosis and therapeutic follow-up, and finally the modalities of treating and preventing haemorrhagic events.

Acquired FXIII deficiency, which has multiple aetiologies and is poorly understood, will not be discussed in this review. Acquired deficiencies due to lack of hepatic synthesis of the FXIII-B subunit (hepatitis, acute hepatic failure) have been described, as have FXIII deficiencies related to consumption in leukaemia, inflammatory colic disease, sepsis and polytrauma. In these cases, FXIII levels are usually only slightly decreased, in the order of 30 to 70%, and the reason for this deficiency in bleeding complications remains to be proven [3].

Structure and function of factor XIII (*figure 1*)Q1

FXIII, or fibrin stabilizing factor, is an intracellular protein that circulates in the blood and increases clot resistance at the very end of the coagulation cascade. It also plays a role in angiogenesis and in maintaining pregnancy [4-7].

In plasma, FXIII circulates as a transglutaminase (FXIII-A_2B_2), consisting of two catalytic A subunits (FXIII-A_2) and two non-catalytic B subunits (FXIII-B_2).

– Subunit XIII-A in the plasma is synthesized by the liver, monocytes and megakaryocytes, and carries the catalytic activity of FXIII (transglutaminase active site). It is present in the form of a FXIII-A2 dimer in platelets and megakaryocytes. Its presence in plasma is thought to be derived from lysis of platelets and monocytic cells.

– Subunit XIII-B is synthesised and secreted by the hepatocyte**.** It has a role in transporting and stabilising the XIII-A subunit in plasma.

After activation by thrombin and calcium in the plasma, separation of the FXIII-B subunits allows for activation of FXIII-A_2, which is then accessible to substrates. The role of factor XIII is to increase clot resistance through several mechanisms:

– by forming covalent bonds between the fibrin monomers α and γ,
– by catalysing the binding of α2-antiplasmin to fibrin, allowing resistance to fibrinolysis by promoting the repair of damaged tissue,
– by binding of the fibrin clot to proteins of the subendothelium (fibronectin, vitronectin, collagen) [7].

Aside from its role in structuring and forming fibrin, FXIII is believed to play other roles in terms of extracellular matrix formation, angiogenesis, and tissue

FIGURE 1

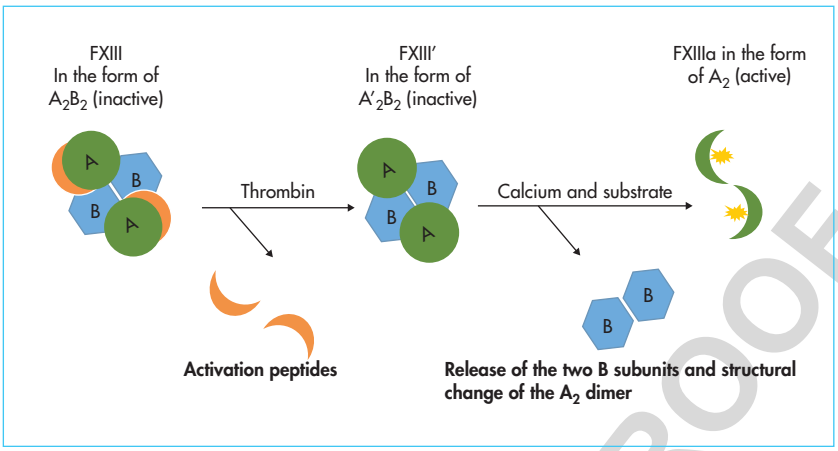

Diagram showing the mechanism of activation of FXIII (from Hsieh *et al.* [7]).
Schéma du mécanisme d'activation du FXIII (d'après Hsieh *et al.* [7]).

remodelling and healing. It is believed to be involved in interactions with inflammatory cells and the complement system [7, 8].

Finally, FXIII is indispensable for maintaining pregnancy. In the presence of fibrin and fibronectin, FXIII is present in the Nitabuch Layer, the area where the placenta separates during delivery. FXIII helps to maintain the integrity of this layer. Conversely, FXIII deficiency decreases the role of this layer in immune tolerance which contributes to foetal losses associated with its deficiency [9, 10].

Two genes encode the two subunits of FXIII. The *F13A1* gene encodes the FXIII-A subunit; a 160-kb gene with 15 exons (and 14 introns) located on chromosome 6 (p24-25) that encodes for a mature protein of 731 amino acids. The *F13B* gene encodes the FXIII-B subunit; a 28-kb gene with 12 exons (and 11 introns) located on chromosome 1 (q31-32) that encodes a mature protein of 641 amino acids [11-13].

Congenital FXIII deficiency may affect either subunit A or B The International Society for Thrombosis and Haemostasis (ISTH) has proposed a classification according to the type of deficiency: subunit A deficiency may be quantitative (type 1) or qualitative (type 2). Subunit B deficiency, which is quantitative only, often has a less severe clinical presentation [3, 7].

Severe forms of this autosomal recessive deficiency are more common in countries with high consanguinity. The Human Gene Mutation Database (HGMD Professional) includes 203 mutations, of which more than 90% are present in the *F13A1* gene and only 20 mutations in the *F13B* gene. These are mainly missense/nonsense mutations in the *F13A1* gene, as well as small deletions/insertions and splice site mutations. Only five large deletions and one large duplication involving one or more exons in the *F13A1* have been identified [14].

Clinical manifestations

Congenital FXIII deficiency may lead to two types of clinical manifestations:

– life-threatening bleeding complications,
– difficulties in carrying a pregnancy to term due to repeated miscarriages.

Severe forms of FXIII deficiency are revealed in 80% of cases due to haemorrhage that occurs when the umbilical cord becomes detached during the neonatal period and in 30% of cases due to spontaneous intracranial haemorrhage (ICH) [2].

Studies reporting less severe deficiencies, also reported other, less severe induced bleeding. A published series of 104 patients with deficiencies ranging from 5% to 30% (85% with FXIII level <5%, 11% with a level at 5-10%, and 4% with a level at 0-30%) reported haemorrhaging of the umbilical cord in 56%, ICHs in 34%, and post-surgical haemorrhaging in 40%, as well as sub-cutaneous haemorrhaging in 57% and muscular haematomas in 49% [1]. Based on the international Rare Bleeding Disorders Database (RBDD), bleeding such as intramuscular haematomas, haemarthrosis, ICH and gastrointestinal (GI) haemorrhages were reported when FXIII plasma activity was between 0 and 10.9%. In this database, these severe haemorrhages (Grade III) were noted in 48.5% of cases [15]. When rates averaged 2.6% (0-23.7%), moderate bleeding was reported, such as ecchymosis, gingivorrhagia, epistaxis, and menometrorrhagia. Finally, when FXIII levels averaged 16.8% (0-37.1%), only bleeding complications -either post-traumatic or when taking anticoagulant or antiaggregant treatment- were reported [15].
Another retrospective study showed that in 27 newborn babies, the early diagnosis of FXIII deficiency was made before the onset of ICH in 48% of cases [17].
A study on a French cohort focused on the clinical expression of severe forms, showing data identical to that of previous studies. Of the 33 patients included with FXIII <10%, 88% had haemorrhagic manifestations, of which 65% were haemorrhages associated with detachment of the umbilical and 31% were ICHs [18].
Some authors have recently suggested using a clinical score, such as the ISTH-BAT, as this has demonstrated a very good correlation between a high score and the number of severe haemorrhagic episodes [19]. However, the relevance of such a score in terms of the diagnosis and management of the deficiency remains to be demonstrated.
Finally, in women, congenital FXIII deficiency is associated with a high frequency of foetal loss, and the value of prophylactic treatment in order to maintain pregnancy has been highlighted in a recent review [20]. In a French retrospective series of 11 women with severe FXIII deficiency (level < 10%), in the absence of prophylactic treatment, four of the women experienced 30 miscarriages, occurring in the first trimester in 97% of cases (one woman had 12 miscarriages). In this study, only two of 11 (18%) patients receiving treatment described menorrhagia, while 27% of women did not experience menorrhagia prior to treatment [21].
The plasma level of FXIII is therefore a critical factor in assessing the risk of haemorrhage, as severe haemorrhagic manifestations are reported for severe deficits. There are currently discussions among experts regarding the minimum level of FXIII required to prevent spontaneous bleeding [16, 22, 23]. These discussions should also take into account FXIII assay methods for diagnosis and therapy, as these methods have evolved in recent years but still represent a real challenge and remain the responsibility of specialised laboratories [24].

Biological diagnosis

Until very recently, FXIII assay methods were based on tests with poor reproducibility and low sensitivity when it came to measuring low levels.
As a reminder, since FXIII occurs after initial clot formation, FXIII deficiency is not detected by standard tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT). Biological diagnosis is only possible after specific measurement of the level of FXIII and medical history and suggestive clinical signs have been obtained. Several biological tests are available, which allow for both diagnosis and therapeutic follow-up of patients with FXIII deficiency. Among the various techniques available, a distinction must be made between functional and antigenic tests. The ISTH international recommendations recommend first-line

screening using quantitative functional FXIII measurement techniques, followed by antigenic techniques to determine the type of deficiency [4].

Functional tests

FXIII functional activity assays remain the gold standard, but are limited by their lack of standardisation and specificity. These include:

– The clot solubility assay, performed in a 5M urea solution or 1% monochloroacetic acid solution. This is a non-standardised test and only detects deficiencies of less than 5%. It is generally no longer practised in French laboratories.
– The ammonia release assay. This is fast, well standardised and can be automated, but is not very sensitive.
– The amine incorporation assay is sensitive, but is time-consuming and cannot be automated or standardised [25].
– The chromogenic method, an automated technique widely used in laboratories, but lacks the sensitivity to detect low levels of FXIII [1, 26].

Antigen tests

Antigen tests are needed to determine the type of deficiency.
Immunological techniques to measure the level of FXIII-A, FXIII-B and the FXIII-A_2B_2 complex are available. More recently, quantitative techniques for antigenic FXIII-A assays have been developed.

– The FXIII-A subunit ELISA technique is the most widely used and correlates well with FXIII activity rates [26].
– An automated technique to measure FXIII-A antigen using latex particles has demonstrated excellent correlation with the functional measurement of FXIII as well as a detection threshold of $< 4\%$ [1, 27].

The low incidence of congenital deficiency thus raises the question of choice of technique used by laboratories. The need to screen for this rare deficiency in clinical situations in which a haemorrhage may be life-threatening should prompt the need for sensitive, standardised and automated techniques. Similarly, improvements in the detection threshold should facilitate the therapeutic follow-up of patients receiving prophylactic treatment. Before techniques with a low detection threshold were available to meet this objective, our team demonstrated the value of using thromboelastometry to adjust the doses of FXIII concentrates for patients with severe FXIII deficiency. Normalisation of parameters such as the lysis index at 60 minutes (LI60) or maximum clot firmness (MCF) has made it possible to objectify therapeutic efficacy, allowing doses to be spaced apart, particularly for patients who have developed an anti-FXIII antibody [28, 29].
Finally, in the absence of recommendations, the use of an automated antigenic technique would appear to be the most suitable for the rapid diagnosis of a deficiency and the therapeutic follow-up of patients.

Molecular biology

Molecular biology testing for a genetic abnormality should be performed in patients with severe FXIII deficiencies and may be proposed for parents and siblings.
Antenatal screening is currently not performed due to the: rarity of the deficiency, approval required to carry out such screening, poorly known haemorrhagic risk of the procedure, existence of a simple blood test that can be carried out at birth in order to make the diagnosis, as well as existence of prophylactic treatment that significantly reduces symptoms and potential complications of the disease.

Treatments

Various treatment regimens are available for the curative or preventive treatment of severe FXIII deficiency. The half-life of FXIII *in vivo* is 11 to 14 days, allowing for the administration of FXIII concentrates in doses that are relatively well spaced. There are two types of drugs:

– a plasma-derived concentrate (pFXIII): Fibrogammin®, from CLS-Behring (Marburg, Germany);
– a recombinant concentrate (rFXIII): Catridecacog® or Novothirteen®, from Novonordisk (Healthcare AG, Switzerland), not available in France.

In cases of acute haemorrhage, especially intracerebral bleeding, the initial dose should be 20-40 IU/kg for pFXIII. The expected recovery rate is 2 IU/dL per 1 IU/kg injected. For rFXIII, the dose is similar, at 35 IU/kg with a recovery rate of 1.7 IU/dL per 1 IU/kg injected [30-32]. In this emergency situation, in the absence of availability of FXIII concentrate, fresh frozen plasma treatment should be administered at a dose of 20 mL/kg.
It is currently accepted that prophylactic treatment should be offered routinely to patients with severe deficiencies. Most recommendations suggest one pFXIII dose of 20-40 IU/kg or 35 IU/kg rFXIII, every four weeks.
There is currently no agreement around the modalities of prophylactic treatment. The timing and pace of initiation of prophylactic treatment as well as the minimum level of FXIII, that defines "severe deficiency" justifying prophylactic treatment, are also debated. Treatment regimens differ according to recommendations, ranging from 10 IU/kg every four to six weeks to 40 IU/kg every four weeks [33-35].
The RBDD proposes treating patients with a level of <15% after the first haemorrhagic episode [36]. The objective of the treatment is to maintain a residual FXIII level >30%. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) recommends long-term prophylaxis in patients with FXIII plasma activity <10%, with a personal or family history of haemorrhage, in order to achieve a residual activity of between 10 and 20% [31]. Recently published data based on the FranceCoag registry confirm the value of introducing prophylactic treatment at an early stage, from the time of diagnosis. In this series of a total of 33 patients with FXIII deficiency <10%, seven of the 15 patients (50%) developed ICH after diagnosis [18].
Finally, authors from Iran have demonstrated efficacy of prophylactic treatment in patients with severe deficiency (<4%), in whom doses of 10 to 26 IU/kg were administered every four to six weeks [37], advocating early screening and early introduction of prophylaxis [17].
The controversy over the minimum residual level of FXIII required to prevent risk of haemorrhage and indicate prophylaxis, which is between 4 and 15%, is also a consequence of the difficulties regarding sensitive and standardised assay methods [16, 22, 23]. The definition of this level and determination of the threshold necessary to prevent the risk of serious haemorrhage may only be possible based on prospective studies using assay techniques, such as antigenic methods with good analytical quality.
Similarly, this threshold is also still under discussion with regard to therapeutic management during pregnancy. The value of prophylactic treatment to prevent systematic early miscarriage in women with severe deficiencies has been clearly demonstrated [20], but, similarly, the level of the residual factor is still debated. A review published in 2018 proposed maintaining a residual level >10-20% until 22 weeks of gestation and then bringing the injections closer together every two to three weeks to maintain a level >30% [30]. Other authors propose a dose of 250 IU/week up to 23 weeks of amenorrhea, then 500 IU/week to term, and

finally a dose of 1,000 IU during labour, with a target residual level of 12% during pregnancy and 35% during labour [37].
A recent French retrospective series showed that 13 pregnancies in nine women were carried to term, 12 of them without haemorrhagic complications under prophylaxis. Doses ranged from 400 to 1,250 IU/week and the injection rate varied from one injection every two weeks to one injection every four weeks. An increase in dose or rate was reported in only three pregnancies. The risk of haemorrhage during labour and postpartum (five vaginal deliveries and six Caesarean sections) was prevented by a single bolus of 1,250 IU [21]. In this series, none of the women received epidural anaesthesia. In the absence of published data and due to the rarity of the deficit, epidurals are not to be recommended.

Monitoring treatment

Residual FXIII levels may be used: to adjust the dose and timing of injections at the start of prophylaxis, throughout follow-up to adjust treatment to body weight, during pregnancy, or in the event of emergency intervention to guide further treatment.
As with other coagulation factor deficiencies, complications related to prophylactic treatment include potential risks of transmission of emerging infectious agents, due to the plasma nature of FXIII concentrates, and the development of alloantibodies against treatment. However, the latter complication is extremely rare in FXIII deficiency. Of the seven cases described in the literature, alloantibodies appeared after 2-13 months of therapy targeting the subunit A in four women. In another case of a 73-year-old patient, alloantibodies appeared one year after the start of therapy directed against the B subunit. A further case of alloantibodies (target not specified) occurred after six days of treatment with plasma transfusion in a 22-year-old woman during pregnancy. In one case, the alloantibody was reported to disappear without any details regarding immune tolerance. In our series of three cases of severe FXIII deficiency, neutralisation of alloantibody, that appeared after three months of treatment in a 22-month-old girl, was achieved over several years (11 years) by treatment administered initially twice a week, then once a week, and then gradually spaced out. The detection of alloantibodies remains challenging, as does the therapeutic follow-up [38]. This small series is interesting in that it demonstrates the value of thromboelastometry in determining residual FXIII level which is necessary to prevent possible risk of haemorrhagic recurrence, particularly in the case of alloantibodies [29].

Follow-up

As with all patients with a rare coagulation factor deficiency, as soon as diagnosis is complete and treatment is initiated, the patient should be followed by a physician specialised in haemostasis. This follow-up should involve a multidisciplinary team from a haemophilia reference centre (*Centre de Référence Hémophilie*, CRH), a haemorrhagic disease resource and skills centre (*Centre de Ressources et de Compétences Maladies Hémorragiques Constitutionnelles*, CRC-MHC) and a haemophilia treatment centre (*Centre de Traitement de l'Hémophilie*, CTH), including a physician, registered nurse, pharmacist, biologist, doctor specialising in physical medicine, clinical geneticist, secretary as needed, as well as independent professionals such as a GP, paediatrician, physical therapist, and nurse or district nurse. The objectives of patient follow-up are to monitor the efficacy and tolerance of treatment, to prevent and detect early complications, and to continue therapeutic education with the patient and/or family, with the aim of promoting compliance with treatment and autonomy.
As soon as the diagnosis is made, a card indicating a blood deficiency should be issued to the patient, stating the type of deficiency, the treatment received, and the

contact details of the referring doctor and follow-up centre (emergency numbers). This card and the treatment follow-up booklet must be regularly updated.

Conclusion

The diagnosis and treatment of severe FXIII deficiency remains challenging. Despite its very low prevalence, the occurrence of haemorrhage when the umbilical cord becomes detached and/or intracerebral haemorrhage should evoke the diagnosis using standard age-matched coagulation tests. FXIII analysis using an easily available, standardised, sensitive and, if possible, automated technique should allow specific treatment, such as FXIII concentrates, to be initiated. The diagnosis of severe FXIII deficiency should also allow prophylactic treatment to begin, which will prevent possible risk of severe haemorrhagic complications (ICH) in 100% of cases and allow women to carry pregnancies to term.]

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