Congenital Factor XIII Deficiency, Diagnosis, and Management

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14.1 Introduction

Congenital factor XIII (FXIII) deficiency is an ultra-rare hemorrhagic disorder with an estimated incidence of one per two million in the general population [1]. The disorder is more frequent in areas with high rates of consanguinity, such as Iran, India, and Pakistan. In a recent study in southeast Iran, a prevalence of 0.2% homozygotes and 3% heterozygotes was found, named Khash FXIII [2]. FXIII deficiency, with an overall mortality rate of ~15% due to intracranial hemorrhage (ICH), umbilical cord bleeding (UCB), and miscarriage, is one of the most severe congenital hemorrhagic disorders [3]. Indeed, in the absence of a prophylaxis program, approximately one-third of patients experience fatal ICH prior to the onset of middle age [1, 3]. Therefore, primary prophylaxis is mandatory for all patients with severe FXIII (FXIII activity <5%) upon diagnosis [4]. Early diagnosis, performed by an FXIII functional assay, and timely management of the disorder are crucial [4, 5]. In the absence of this assay in a considerable number of laboratories, a traditional clot solubility test is the only diagnostic test for the detection of FXIII deficiency [6]. Primary prophylaxis can be provided using a wide range of therapeutic agents, including traditional choices, fresh frozen plasma (FFP), cryoprecipitate, or the more advanced options of plasma-derived FXIII and recombinant FXIII concentrates [7, 8]. Although the rate of life-threatening bleeding is high in FXIII deficiency, with timely diagnosis and appropriate therapeutic regimen, the rate of morbidity and mortality can be significantly reduced. Clinical presentations, family history, and laboratory findings should be used for timely diagnosis, and the most suitable therapeutic regimen should be instituted for proper management of the disorder.

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14.2 Classification

Coagulation FXIII is a heterotetramer (FXIII-A_2B_2) composed of two catalytic (FXIII-A_2) and two carrier subunits (FXIII-B_2) that are encoded by two separate genes, *F13A* and *F13B* [9]. Depending on the underlying gene defect, FXIII is classified into two types: FXIII-A and FXIII-B deficiencies [9, 10]. Due to the carrier role of FXIII-B_2, the deficiency of this FXIII subunit is accompanied by mild bleeding episodes. On the other hand, FXIII-A deficiency is one of the most severe congenital bleeding disorders, which is further classified into type I, with a concomitant decrease in FXIII-A antigen and activity levels, and type II FXIII-A deficiency, with normal or near-normal FXIII antigen levels and decreased FXIII activity [5] (Table 14.1).

Table 14.1 Classification of congenital factor XIII deficiency (adapted from [5])

FXIII deficiency		FXIII-A antigen	FXIII-B antigen	FXIII-A_2B_2 antigen	FXIII activity	Platelet FXIII-A antigen	Platelet FXIII activity
FXIII-A deficiency	Type I	↓↓↓	>30%	↓↓↓	↓↓↓	↓↓↓	↓↓↓
	Type II	↓ OR N	>30%	↓ OR N	↓↓↓	↓ OR N	↓↓↓
FXIII-B deficiency		↓↓	↓↓↓	↓↓↓	↓↓	N	N

The classification is based on the recommendations of the Scientific and Standardization Committee (SSC), Factor XIII and Fibrinogen Subcommittee, International Society for Thrombosis and Haemostasis (ISTH). *N* normal

14.3 Clinical Manifestations

Patients with congenital FXIII deficiency present a wide range of clinical manifestations, including UCB, ICH, impaired wound healing, epistaxis, gum bleeding, etc. UCB is a hallmark of FXIII deficiency and afibrinogenemia and is the most common presentation, observed in about 80% of neonates with severe FXIII deficiency [11]. In the absence of timely diagnosis and appropriate management, FXIII deficiency can result in fatal consequences in a considerable number of such neonates [2]. ICH is the most dreaded occurrence, and the main cause of death, in FXIII deficiency, observed in approximately one-third of patients [3]. In fact, ICH is more common in FXIII deficiency than any other congenital bleeding disorder [12, 13]. Generally, ICH has two main consequences: death and neurological complications. Most often (>90%), ICH occurs intraparenchymally, with the rest located in epidural and subdural spaces [3]. In about two-thirds of patients, ICH causes neurological complications, some of which are serious and disruptive to the patient's life [3]. ICH can occur spontaneously or following minor head trauma. Trauma-related ICH is more common in children, while spontaneous ICH is more frequent in adults [3]. Recurrent miscarriage is a common finding in women with severe FXIII deficiency, and generally, these women cannot have a successful delivery in the absence of replacement therapy [3, 14]. In one study, about one-third of patients experienced recurrent miscarriages, with two patients experiencing 13 spontaneous abortions each. Another interesting finding of this study was the high rate of mortality due to UCB: about one-fifth of deaths [3]. Due to the crucial role of coagulation FXIII in the healing process, impaired wound healing is a relatively common finding; about one-third of patients experience this diathesis [15–18] (Table 14.2).

Although heterozygous individuals are generally asymptomatic, post-traumatic bleeding has been reported in these individuals more frequently than in the general population. Indeed, heterozygous FXIII deficiency is mainly a hemorrhagic complication for women experiencing hemostatic challenges. Spontaneous bleeding does not occur in heterozygous FXIII deficiency, and almost all bleeding events occur in hemostatic challenges such as pregnancy, surgery, childbirth, and trauma. Among individuals with heterozygous FXIII deficiency, postoperative bleeding, postpartum hemorrhage, and miscarriage are the most common presentations [19–24].

Table 14.2 Clinical manifestations of patients with congenital factor XIII deficiency [15–18]

	Dorgalaleh et al. (N:218)[a]	Bouttefroy et al. (N:33)	Ivaskevicius V et al. (N:104)	Shetty et al. (N:96)
Umbilical cord bleeding	82.5%	57.6%	56%	73%
Intracranial hemorrhage	17%	27.3%	34%	19%
Miscarriage	~10%	3%[b]	NR	NR
Hematoma	53%	15.2%	49%	30%
Ecchymosis	13%	15.2%	NR[e]	58%
Hemarthrosis	4%	3%	36%	7%
Delayed wound healing	31%	NR	29%[d]	NR
Postsurgical bleeding	3%	3%[c]	40%	19%
Gum bleeding	17%	6%	NR	13%
GI bleeding	NR	NR	6%	4%
Menorrhagia	5%	3%[f]	NR	94%
Epistaxis	14%	NR	NR	25%
Genitourinary tract bleeding	NR	NR	NR	15%
Lacerations	NR	NR	NR	89%

NR Not reported
[a] Combination of several Iranian reports
[b] Spontaneous abortion
[c] Bleeding during surgery
[d] Prolonged wound bleeding
[e] Subcutaneous: 57%
[f] Menometrorrhagia

14.4 Molecular Basis

Severe congenital FXIII-A deficiency is due to homozygote or compound heterozygote *F13A* gene variants, while FXIII-B deficiency is due to *F13B* gene variants [9]. These variants can affect the synthesis of the protein, decrease its stability, and subsequently cause intracellular degradation of the protein [9, 21, 25, 26]. A total of 172 variants have been reported in the *F13A* gene, while 25 variants have been observed within *F13B*. About half of the variants in *F13A* (48.8%) and *F13B* (52%) genes are missense; most *F13A* variants (55.3%) occur within the catalytic core [9, 21, 28–30] (Table 14.3).

While there is no hotspot for *F13A* and *F13B* genes, a few recurrent variants have been reported in different nationalities [9]. Although Sanger sequencing is the most commonly available molecular method, in 5% of cases it cannot detect the underlying variant(s). However, next-generation sequencing or high-throughput sequencing can improve this situation [9]. The spectrum of *F13* gene variants in heterozygous FXIII deficiency is similar to that of homozygote FXIII deficiency. A total of 49 variants have beendetected in heterozygous FXIII deficiency, most of them missense (n:30, 61.2%), nonsense (n:6, 12.2%), small deletions (n:6, 12.2%), splice site (n:4, 8.2%), and large deletions (n:3, 6.2%) [21, 25–36].

Table 14.3 Spectrum of *F13A* and *F13B* gene variants (adapted from [9])

Gene	Number of variants	Type of variants (number)	Exonic site (number)	Protein site (number)	Comment
F13A	172	Missense (84) Insertion/deletion (45) Splice site (25) Nonsense (18)	Intronic (23) Exon 2 (6) Exon 3 (13) Exon 4 (14) Exon 5 (11) Exon 6 (13) Exon 7 (15) Exon 8 (8) Exon 9 (14) Exon 10 (7) Exon 11 (6) Exon 12 (11) Exon 13 (5) Exon 14 (13) Exon 15 (10)	Catalytic core (95) Beta sandwich (27) Barrel-1 (12) Barrel-2 (26) Undetermined (12)	
F13B	25	Missense (13) Splice site (4) Frameshift (8)	Intronic (4) Exon 2 (1) Exon 3 (3) Exon 4 (1) Exon 5 (1) Exon 7 (2) Exon 8 (3) Exon 9 (1) Exon 12 (1) Undetermined (8)	Sushi 1 (2) Sushi 2 (3) Sushi 3 (2) Sushi 4 (3) Sushi 6 (2) Sushi 7 (4) Sushi 8 (1) Sushi 12 (1) Undetermined (7)	

14.5 Diagnosis

Routine coagulation laboratory tests, including bleeding time, prothrombin time, activated partial thromboplastin time, thrombin time, and platelet count, are normal in FXIII deficiency [37–41]. Therefore, a more specific test should be used for the detection and confirmation of FXIII deficiency [42–47]. Although the clot solubility test is not a standard procedure, and is not further recommended for the detection of FXIII deficiency, it is the most commonly used diagnostic test worldwide and is used as a primary screening test in most developing, and 20% of developed, countries [46, 48]. In this assay, fibrin clot solubility is assessed in 5 M urea, 2% acetic acid, or 1% monochloroacetic acid solutions. In normal samples, the clot is stable for 1 day or more, whereas in FXIII-deficient samples, the clot is dissolved within a few minutes to a maximum of 1 h [37, 46]. The clot solubility test is not standardized, and various parameters influence the assay, including the type and concentration of clotting agent, the time of clotting, the type and concentration of solubilizing agents, and the time of detection of solubility [37, 46].

Precise diagnosis and classification of FXIII deficiency are achieved through quantitative assays. These are based on two principles: (1) measurement of FXIII activity level (functional activity assays) and (2) measurement of FXIII antigen level (immunological assays). FXIII activity assay is able to detect acquired and inherited forms of the disease and can quantify the FXIII level [4, 37]. Functional FXIII assay, which is used as a first-line assay for diagnosis, measures the residual FXIII activity. The measurement of FXIII activity is conducted through methods such as ammonia-release assay, or amine incorporation assay [37], which the former is the most commonly used assay. In this test, activated FXIII (FXIIIa) crosslinks a substrate to an oligonucleotide, which contains glutamine. Then, via glutamate dehydrogenase-mediated indicator reaction, NADH or NADPH in combination with one molecule of ammonia is released. FXIII activity is determined by the photometric absorbance at 340-nm wavelength. At a low FXIII activity level, photometric absorbance at 340 nm is decreased [37] (Fig. 14.1).

Due to the presence of other ammonia-producing and NADH-consuming reactions independent of FXIIIa, the use of a plasma blank is necessary to avoid overestimation of FXIII activity level [37, 45]. Since patients with a lower level experience severe clinical manifestations, the application of a plasma blank, for more reliable measurement of low FXIII activity, is inevitable [37]. FXIII antigen assay can be used for the classification of FXIII deficiency. There are several methods of measuring antigen levels, among which enzyme-linked immunosorbent assay is the most sensitive and reliable [37, 47]. One of the most important limitations of the assay is that it cannot identify type II FXIII deficiency [37].

Based on Clinical and Laboratory Standards Institute (CLSI) guidelines, three points should be considered for FXIII antigen assay: (1) interference of non-complex FXIII-B in the FXIII-A_2B_2 antigen assay should be prevented; (2) in subunit

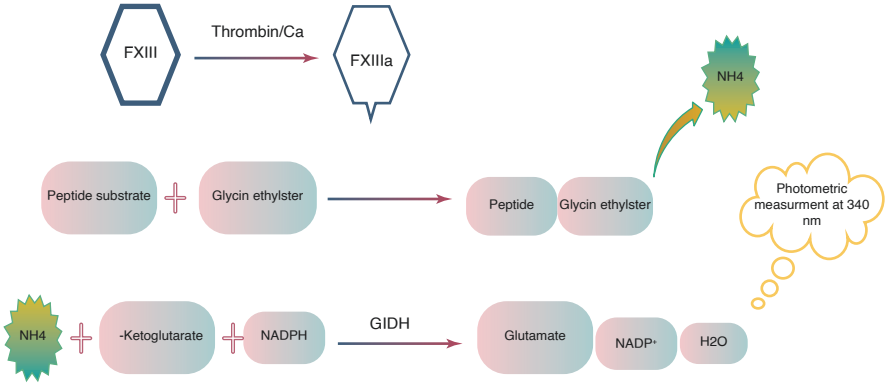

Fig. 14.1 The principle of the ammonia-release FXIII activity assay. Following activation, FXIIIa crosslinks a substrate to a glutamine-containing oligonucleotide, which releases NADH or NADPH with one molecule of ammonia via GIDH reaction. Finally, photometric absorbance at 3400 nm demonstrates FXIII activity. *FXIII* factor XIII; *FXIIIa* activated factor XIII; *GIDH* glutamate dehydrogenase-mediated indicator; *NADPH* nicotinamide adenine dinucleotide phosphate; *nm* nanometer

assays, both free and complex antigenic forms should react with antibodies to the same extent; and (3) interference of fibrinogen concentration in the antigen assay should be prevented [1].

A low level of FXIII in plasma does not necessarily result from congenital FXIII deficiency, as it can be related to an antibody against FXIII or other acquired conditions [49–53]. There are two types of autoantibodies, including neutralizing, which inhibits the activation of FXIIIa, and non-neutralizing, which accelerates the elimination of FXIIIa from the circulation. The former can be detected by a mixing study, while the latter can be diagnosed by a binding assay [54–57]. Neutralizing anti-FXIII-A antibodies cause a significant decrease in FXIII activity, whereas FXIII-A_2 and FXIII-A_2B_2 antigen levels are normal or slightly decreased. In contrast to neutralizing, non-neutralizing antibodies result in a significant reduction in all these parameters. In the presence of neutralizing and non-neutralizing anti-FXIII-A antibodies, the plasma FXIII-B_2 antigen level is more than 30%. In the presence of an anti-FXIII-B antibody, there is a reduction of FXIII-A and FXIII-A_2B_2 levels with a considerable reduction in FXIII-B_2 antigen [37] (Fig. 14.2).

A Bethesda assay is performed in order to achieve the approximate quantification of the inhibitors against FXIII. The Nijmegen modification of the Bethesda assay has more sensitivity and specificity compared with the Bethesda assay alone. If the residual FXIII activity is <25%, further dilution is recommended. Moreover, FXIII activity >75% excludes the presence of an inhibitor [26, 27]. An inhibitor level ≥0.6 BU/mL is considered to be of clinical significance. In addition, inhibitor levels are defined as low responding (‘5 BU/mL) and high responding (≥5 BU/mL) [37, 58].

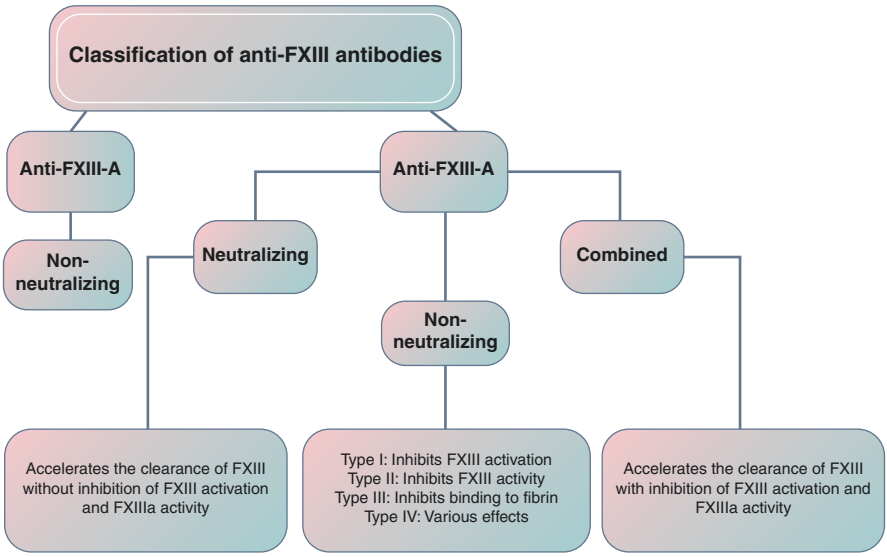

Fig. 14.2 The classification of different types of anti-factor XIII antibodies. *FXIII* factor XIII; *FXIIIa* activated factor XIII

14.6 Management

Due to the high rate of life-endangering hemorrhages, particularly ICH, primary life-long prophylaxis from the moment of diagnosis is mandatory for all patients with severe congenital FXIII deficiency [1, 4, 59]. Several therapeutic options are available, including FFP, cryoprecipitate, plasma-derived FXIII concentrate, and recombinant FXIII-A_2 (rFXIII-A_2) concentrate [59–65]. In spite of the severity of FXIII deficiency and its high rate of life-threatening bleeding, it can be managed easily due to the long half-life of FXIII (11–14 days) and its low hemostatic level. Although the treatment is relatively easy, however, treatment abandonment may result in fatal ICH in a considerable number of patients, who should be warned about this possibility [3]. Precise hemostatic levels of FXIII that prevent spontaneous major and minor bleeding, and manage major and minor surgeries, are not clear. Although plasma-derived FXIII and rFXIII are the preferred options, FFP and cryoprecipitate are the only therapeutic choices in a considerable number of countries. All available options are discussed below [60, 61] (Table 14.4).

For prophylaxis in FXIII deficiency, both 10–26 IU/kg every 4–6 weeks and 40 IU/kg every 4 weeks have been successfully used, but the rate of bleeding episodes was lower in the latter regimen. For surgical management of patients, a dose range from 25 to 40 IU/kg was used [64]. For the management of FXIII deficiency, rFXIII-A_2, in a dose of 35 IU/kg every 4 weeks, significantly reduced the rate of

Table 14.4 Therapeutic regimens for management of patients with congenital factor XIII deficiency (adapted from [15])

Therapeutic option	Type of treatment	Dose	Intervals
FFP	Prophylaxis	10 mL/kg	Every 4–6 weeks
Cryoprecipitate		1 bag/10 kg	
Pd-FXIII concentrate		10–26 IU/kg	
		40 IU/kg	Every 4 weeks
rFXIII-A_2 concentrate		35 IU/kg	Every 4 weeks
Pd-FXIII concentrate	ICH	1. Initially 30 IU/kg 2. 10–26 IU/kg for 10 days	
Pd-FXIII concentrate	Successfully delivery	1. 12 IU/dL (range 3–70 IU/dL) during pregnancy 2. 35 IU/dL (range 19–62 IU/dL) during labor 3. 10 IU/kg for 2 weeks	
Tranexamic acid	Minor surgery	15–20 mg/kg or 1 g	Four times daily alone
Pd-FXIII concentrate	Major surgery	10–40 IU/kg	Depending on the interval since the last prophylaxis and severity of bleeding
Pd-FXIII concentrate	PPH	1. 250 IU weekly early in pregnancy until 23rd week 2. 500 IU per week 3. For labor and delivery, a booster dose of 1000	

FFP fresh frozen plasma; *Pd-FXIII concentrate* plasma-derived factor XIII concentrate; *ICH* intracranial hemorrhage; *rFXIII* recombinant factor XIII; *PPH* postpartum hemorrhage; *IU* international units; *kg* kilogram

bleeding [65]. With the administration of this dose, the trough level of FXIII activity remained above 10% in all patients with congenital FXIII-A deficiency [65, 66]. Interestingly, the assay was performed in these patients in the absence of a plasma blank, meaning that the through level of FXIII activity was overestimated by about 5–8% of real FXIII activity levels [4]. It means that even a very low plasma level of FXIII (probably 5%) is sufficient to prevent bleeding [11].

Management of surgery is a challenge in FXIII deficiency, and separate therapeutic doses have been proposed for major and minor surgeries. It should be kept in mind that the management of surgical interventions can be affected by a number of elements and the same hemostatic level target cannot be used for all types of minor, and especially major, surgeries [15]. These include type, duration, and complexity of surgery [64]. A wide range of FXIII-level targets, ranging from 5% to >100%, has been proposed [15, 64, 67]. However, during prolonged and complicated surgeries, an FXIII level even as high as >100% cannot guarantee hemorrhagic prevention. Therefore, close monitoring of patients, especially by determination of FXIII activity during surgery, should be a matter of course for the prevention of intraoperative hemorrhage and related consequences. Close collaboration between hematologist, anesthesiologist, and surgeon is thus necessary. Although, as expected, the management of minor surgeries is less complex, as simple a developmental process as teething may result in life-threatening bleeding that requires medical intervention and factor replacement therapy [68]. Fadoo et al. recommended a dose of 10–20 U/kg FXIII concentrate for 2–3 days in the case of minor surgeries [69]. Although Curnow et al. recommended only tranexamic acid, with a dose of 15–20 mg/kg for the management of minor surgeries in rare bleeding disorders (RBDs) including FXIII deficiency, it seems that tranexamic acid cannot prevent bleeding in all types of minor surgeries [70]. For dental extraction, as an example, a minimum of 5% of FXIII level in an adult has been shown to be sufficient to prevent bleeding; other studies confirm this [1, 71]. In a large Iranian case series, single doses of 10 IU/kg, 30 IU/kg, and 50 IU/kg FXIII concentrate, respectively, were administered for minor surgery, major surgery or circumcision, and neurosurgery. Although preoperative FXIII activity was not ascertained, this study's authors expected that these doses would increase FXIII levels to 25%, 75%, and >100%, respectively [13]. In the absence of definitive guidelines, management of surgical intervention, especially major, is challenging in patients with congenital FXIII deficiency. With consideration of all risk factors, and close collaboration between medical teams, and close monitoring of the patient during surgery, the risk of intraoperative hemorrhage can be decreased significantly and patients' quality of life can be improved. A suitable therapeutic regimen should prevent intraoperative hemorrhage and promote successful wound healing.

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