Original Article

Access this article online

Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_1_21

Congenital factor XIII deficiency in Iraq: An 8-year single-center study

Afrah A. Salih, Khalid S. Masood, Essam K. Ibraheem

Abstract:

BACKGROUND: Congenital FXIII deficiency is a rare genetic bleeding disorder that is inherited in an autosomal recessive pattern with a frequency of 1/2 million individuals in the human population. Deficiency of FXIII is associated with significant bleeding disorders.

AIMS: This study aimed to evaluate the demographic parameters, clinical presentations, and outcome of patients who were diagnosed with congenital factor XIII deficiency.

SUBJECTS AND METHODS: A retrospective descriptive study of patients who were diagnosed with congenital FXIII deficiency over a period from August 2008 to August 2016 was conducted. The study included patients who were diagnosed by having bleeding tendency and normal standard coagulation tests (normal platelet count, normal prothrombin time; normal partial thromboplastin time, and normal bleeding time) and the diagnosis was confirmed by clot solubility test in 5M urea. The diagnosis was made in the Hemophilia Ward, Children Welfare Teaching Hospital, Medical City, Baghdad.

RESULTS: There were 111 cases of other coagulation factors' deficiency (rare bleeding disorders) registered in the center, congenital FXIII deficiency represented 24 (22%) of them. Males represented 14 (58.3%) and females 10 (41.7%) of patients. Most of the patients (41.7%) had their symptoms during the 1st year of life. Positive consanguinity was found in 100% of patients and 14 (58.3%) patients had a family history of FXIII deficiency. Umbilical cord bleeding and gum bleeding were present in 37.5% and 20.8%, respectively, and they were the most common first presenting symptoms of FXIII-deficient patients, while muscle hematoma (28.5%) and joint bleeding (24.7%) were the most common presenting symptoms in follow-up visits. The majority of the patients (79.1%) did not develop complications, the complications were developed in 3 (12.4%) patients, which were intracranial bleeding in 2 (8.3%) patients and liver hematoma in 1 (4.1%) patient. One patient (4.1%) developed recurrent abortion and one patient (4.1%) developed hepatitis C. No death was reported during the study period.

CONCLUSIONS: FXIII deficiency founded to be a more common rare bleeding disorder among Iraqi patients, with a high rate of consanguineous marriage. Umbilical cord bleeding and gum bleeding were the most common presenting symptoms for FXIII deficiency. There was a considerable delay in the diagnosis of FXIII deficiency in the majority of patients.

Keywords:

Clinical profile of factor XIII deficiency, factor XIII deficiency, outcome of factor XIII

Introduction

Factor XIII (FXIII) is a transglutaminase enzyme that was first discovered as a clotting protein in the coagulation cascade. However, recent literature describes multiple roles for this factor, including the ability to cross-link proteins in the plasma, vascular matrix, endothelial cells, platelets, and monocytes. In addition to maintaining normal hemostasis, FXIII plays a role in atherosclerosis, wound healing, inflammation, and pregnancy.[1,2]

The main role of FXIII-B is to protect FXIII-A2 from proteolytic degradation and inactivation; thereby extending the time,

Department of Pediatrics, Children Welfare Teaching Hospital, Baghdad, Iraq

Address for correspondence:
Dr. Afrah A. Salih, Department of Pediatrics, Children Welfare Teaching Hospital, Baghdad, Iraq.
E-mail: afrahsalih@yahoo.com

Submission: 02-01-2021
Accepted: 10-03-2021
Published: 21-06-2021

How to cite this article: Salih AA, Masood KS, Ibraheem EK. Congenital factor XIII deficiency in Iraq: An 8-year single-center study. Iraqi J Hematol 2021;10:65-8.

FXIII-A2 remains in circulation. Another critical role of FXIII-B is the localization of FXIII to the polymerizing fibrin chains to facilitate cross-linking. FXIII-B is primarily produced in the liver.[3] Plasma FXIII-B specifically binds to the γ′ chain of fibrinogen type 2. Fibrinogen acts as a carrier for FXIII in plasma and helps to downregulate potential cross-linking activity.[4]

Factor XIII deficiency is a rare bleeding disorder with an incidence of 1 per 1–3 million individuals.[5] The inheritance pattern of FXIII deficiency is autosomal recessive, with an expected higher incidence among populations with a high rate of consanguineous marriages. This rare bleeding disorder affects people of all races and genders.[6]

Furthermore, some cases have acquired deficiencies for factor XIII, there are mainly due to drug-induced or an autoimmune disorder.[7]

The aim of the study was to describe the demographic parameters, clinical presentations, and outcome of patients who were diagnosed with congenital factor XIII deficiency in the Hemophilia Ward/Children Welfare Teaching Hospital/Medical City/Baghdad.

Subjects and Methods

This is a retrospective descriptive study of 24 patients (children and adults) who were diagnosed with congenital FXIII deficiency in the Hemophilia Ward, Children Welfare Teaching Hospital, Medical City, Baghdad, over a period of 8 years from August 2008 to August 2016. The demographic and clinical features and treatment have been collected for included patients, and they were diagnosed by having bleeding tendency and normal standard coagulation tests (normal platelet count, normal prothrombin time, normal partial thromboplastin time, and normal bleeding time), and the diagnosis was confirmed by clot solubility test in 5 m urea (qualitative test for FXIII deficiency). All the laboratory tests were performed at the laboratory of the Hemophilia Ward, Children Welfare Teaching Hospital, Medical city, Baghdad.

Statistical analysis

SPSS version 20 (SPSS Inc., Chicago, Ill., USA) was used for data entry and analysis; frequency and percentage were used to represent the categorical data. Chi-square test was used to confirm significance (Fisher's exact test used if Chi-square not applicable). $P \leq 0.05$ was considered significant.

Results

Apart from factor VIII and factor IX deficiencies, 111 cases with other coagulation factors' deficiency (rare bleeding disorders) were registered in the Hemophilia Ward/Children Welfare Teaching Hospital/Medical City/Baghdad [Figure 1].

Regarding congenital FXIII deficiency, it represented 24 (22%) registered rare bleeding disorders.

A total number of 24 FXIII-deficient patients were identified during the study period; there were 14 (58.3%) males and 10 (41.7%) females. Out of these 10 females with factor XIII deficiency, there were five patients who had started menstruation and only one patient was married.

Table 1 demonstrates the demographic feature of all enrolled patients, age at symptoms onset of factor XIII deficiency was compared with the age at laboratory diagnosis.

In only 4 (16.7%) patients, the diagnosis of factor XIII deficiency was made simultaneously (at time of onset of symptoms). There was a considerable delay (months and in some patient-years) in establishing the laboratory diagnosis in the remaining patients (patients were often treated with blood and blood products several times before attending the hemophilia ward/children welfare teaching hospital).

Of the 24 patients included in this study, the family history of FXIII deficiency was positive in 14 (58.3%) patients.

The rate of consanguinity among parents of the patients was 100%; 37.5% were first cousins.

The most common first presenting symptom of factor XIII deficiency patients was umbilical cord bleeding

Table 1: Factor XIII-deficient patient's characteristics (*n*=24)

Variables	*n* (%)
Age at symptoms onset (years)	
<1	10 (41.70)
1-<5	9 (37.50)
5-10	1 (4.20)
>10	4 (16.60%)
Age at laboratory diagnosis (years)	
<1	10 (41.7)
1-<5	7 (29.2)
5-10	3 (12.4)
>10	4 (16.7)
Laboratory diagnosis simultaneously	
Yes	4 (16.70)
No	20 (83.30)
Family history	
Yes	14 (58.30)
No	10 (41.70)
Parental consanguinity	
Positive	24 (100.00)

Table 2: Comparison of factor XIII-deficient patient with and without life-threatening bleeding and demographic variables (*n*=24)

Variable	Life-threatening bleeding (*n*=3)		*P**
	Yes, *n* (%)	No, *n* (%)	
Gender			
Female	3 (30.0)	7 (70.0)	0.02
Male	0	14 (100.0)	
Family history of FXIII deficiency			
Yes	0	14 (100.0)	0.02
No	3 (30.0)	7 (70.0)	
Age at onset of symptoms (years)			
<1	2 (20.0)	8 (80.0)	0.3
>1	1 (7.1)	13 (92.9)	
Age at laboratory diagnosis (years)			
<1	3 (30.0)	7 (70.0)	0.02
>1	0	14 (100.0)	
Simultaneously laboratory diagnosis			
Yes	1 (25.0)	3 (75.0)	0.4
No	2 (10.0)	18 (90.0)	

*Fisher's exact test. FXIII=Factor XIII

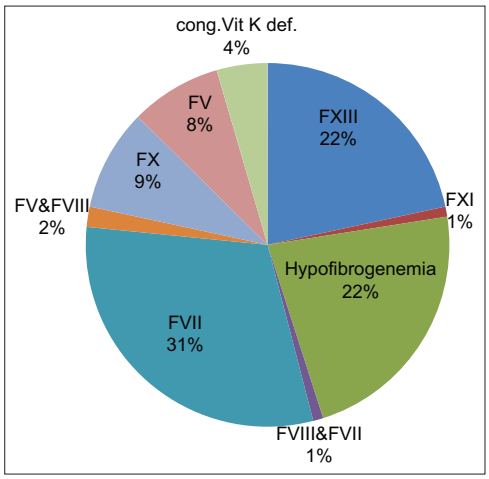

Figure 1: Frequency of rare bleeding disorders in Hemophilia Ward/Children Welfare Teaching Hospital/Medical City/Baghdad

which was observed in 9 (37.5%) patients. Gum bleeding, epistaxis, and skin bleeding were in 5 (20.8%), 3 (12.5%), and 3 (12.5%) patients, respectively, while hematoma, after intramuscular injection, menorrhagia, and prolong wound healing were the first presenting symptoms in only 2 (8.3%), 1 patient (4.2%), and 1 patient (4.2%) patients, respectively.

The most common symptoms of FXIII deficiency were the muscle bleeding after trauma in 53 (28.5%), joint bleeding in 46 (24.7%), skin bleeding in 38 (20.4%), and gum bleeding in 27 (14.5%) patients, and other symptoms included hematuria in 7 (3.8%), menstrual bleeding in 6 (3.2%), epistaxis in 4 (2.2%), and intracranial hemorrhage in 2 (1.1%) patients. In addition, bleeding after circumcision, scrotal bleeding, and hematoma of the liver were in 1 (0.5%) patient for each symptom. Three (12.5%) patients with factor XIII deficiency developed life-threatening bleeding, two patients had central nervous system (CNS) bleeding, and one patient had hematoma of the liver.

The life-threatening bleeding was found to be significantly higher among female gender and younger age at diagnosis; while it is not significant for age at onset of symptoms and time to diagnosis [Table 2].

Patients' outcomes

- Life-Threatening Bleeding: Two female patients had CNS bleedings, the first one developed intracerebral hemorrhage (ICH) at age of 8 years old after head trauma, now she is 17 years old and she is well. The second one developed ICH at age of 14 years old also after head trauma and now, she is 18 years, also she is well without any sequel. One female developed hematoma of the liver after trauma and presented to our hospital as a case of the acute abdomen when she was 2 years old, now she is 7 years old and she is well
- One married female patient (33 years old) had recurrent abortions (8 times) and she was divorced for that reason
- No death was reported among patients with FXIII deficiency in our center.

Discussion

Over 8 years, 24 patients diagnosed with FXIII deficiency, of all age groups, were included in our study from a single center. Although this congenital deficiency is a rare bleeding disorder globally, the current study consists of 24 patients which is higher than the expected ratio of our region population and that can be attributed to the high frequency of consanguineous marriage in the region and to the autosomal recessive pattern of inheritance of the disease, this is in agreement with Dorgalaleh *et al*.'s study[8] which showed that an approximately 12-fold higher prevalence of FXIII deficiency is estimated in Iran. In this study, the males were found to be more affected than females in (58%), and this is in agreement with Al-Sharif *et al*.'s study[9] which showed that males were affected in 64.8%, Fadoo and Saleem[10] reported that the gender distribution for FXIII deficiency was equal in male and females. Regarding the age of symptoms onset, we found that it was higher in a patient less than 5 years old as 79.2% were affected during this age group (when they start to crawl, walk, and play), which agrees with Fadoo and Saleem's study[10] that showed 90% of patients having symptoms during this period.

We found in this study that only 16.7% of the patients were diagnosed simultaneously at the time the patient developed

the symptoms and 83.3% had a delay in the diagnosis, this delay in the diagnosis of FXIII deficiency could be explained by the fact that the majority of patients were often treated by blood and blood products before attending our center that tends to mask the underlying coagulopathy. In this study, we found that family history of FXIII deficiency in the affected patients was positive in 58.3%. This is in agreement with Al-Sharif *et al*.'study[9] in which family history was positive in 59%, while Fadoo and Saleem[10] reported lower family history (40%) than our results.

Consanguinity plays a major role in the transmission of disease, as in all autosomal recessive disorders, the incidence is more among inter-family marriages; in our study, consanguinity of the parents with FXIII deficiency was 100% and in 37.5% of the cases, the parents were first cousins' patients, Fadoo and Saleem[10] showed that consanguineous marriage was found in 80%.

Regarding symptomatology, we found that the most common presenting symptom for FXIII deficiency was umbilical cord bleedings (37.5%), which agrees with AL-Sharif *et al*.'s study[9] which showed that umbilical cord bleeding was found in 41% of the patients, but this did not agree with Fadoo and Saleem's study[10] who reported that the percentage of umbilical cord bleeding was 20%.

For the follow-up visits, the most common bleeding site was muscle bleeding (28.5%), in another study, Al-Sharif *et al*.[9] reported that ecchymosis was the most common and found in 71% patients, while the Easy disability at different sites were the presenting features in Fadoo and Saleem's study[10] that was found in 80% of the patients.

Joint bleeding was the second most common symptom in our study in 24.7% of patients which agrees with Mansouritorghabeh *et al*.'s study[11] that reported joint bleeding in 36% of patients.

Menorrhagia was found to affect 3.2% of the female patients, while in the study by Mansouritorghabeh *et al*.,[11] 43% of women of reproductive age were affected by this complication.

For life-threatening complications, we had two patients (out of 24 patients) developed intracranial bleeding (8.3%), proved on neuro-imaging, and were managed with fresh frozen plasma, cryoprecipitate, this differs from the results of Al-Sharif *et al*.'s study[9] which showed that 18% of the patients had intracranial, also differs from Fadoo and Saleem[10] results that report intracranial bleeding to affect (20%) of the patients in the study groups.

Twenty-four patients were diagnosed, treated, and followed up in our center, all of them were treated by blood and blood products, just one of them had hepatitis c, and no patient died in this study period.

Limitation of the study

This study relies on urea solubility test as the only test for diagnosis.

Conclusions

- FXIII deficiency is a rare bleeding disorder, but this study revealed that the cases of FXIII deficiency are high in comparison with overall worldwide frequency; a high rate of consanguineous marriage may contribute to this prevalence
- Umbilical cord bleeding and gum bleeding were the most common presenting symptoms for FXIII deficiency

There was a considerable delay in the diagnosis of FXIII deficiency in the majority of patients. (the delay ranges from 3 to 6 months).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Richardson VR, Cordell P, Standeven KF, Carter AM. Substrates of Factor XIII-A: Roles in thrombosis and wound healing. Clin Sci (Lond) 2013;124:123-37.
2. Schroeder V, Kohler HP. New developments in the area of factor XIII. J Thromb Haemost 2013;11:234-44.
3. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: Diagnosis and treatment. Blood 2015;125:2052-61.
4. Mitchell JL, Mutch NJ. Let's cross-link: Diverse functions of the promiscuous cellular transglutaminase factor XIII-A. J Thromb Haemost 2019;17:19-30.
5. Peyvandi F, Palla R, Menegatti M, Siboni SM, Halimeh S, Faeser B, *et al*. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: Results from the European Network of Rare Bleeding Disorders. J Thromb Haemost 2012;10:615-21.
6. Ejaz M, Saleem A, Ali N, Tariq F. Factor XIII deficiency with intracranial haemorrhage. BMJ Case Rep 2019;12:e228682.
7. Ichinose A, Japanese Collaborative Research Group on AH13. Autoimmune acquired factor XIII deficiency due to anti-factor XIII/13 antibodies: A summary of 93 patients. Blood Rev 2017;31:37-45.
8. Dorgalaleh A, Tabibian S, Farshi Y, Hosseini MS, Shams M, Tavasoli B, *et al*. A practical approach in laboratory diagnosis of Factor XIII deficiency. Sci J Iran Blood Transfus Organ 2016;13:348-64.
9. Al-Sharif FZ, Aljurf MD, Al-Momen AM, Ajlan AM, Musa MO, Al-Nounou RM, *et al*. Clinical and laboratory features of congenital factor XIII deficiency. Saudi Med J 2002;23:552-4.
10. Fadoo Z, Saleem AF. Factor XIII deficiency in children – Clinical presentation and outcome. J Coll Physicians Surg Pak 2008;18:565-8.
11. Mansouritorghabeh H, Manavifar L, Banihashem A, Modaresi A, Shirdel A, Shahroudian M, *et al*. An investigation of the spectrum of common and rare inherited coagulation disorders in north-eastern Iran. Blood Transfus 2013;11:233-40.