Short Report

Factor XIII deficiency: Lessons from two patients with unusual bleeding

SUVIR SINGH

ABSTRACT

Factor XIII (FXIII) deficiency is a rare bleeding disorder, characterized by umbilical cord, skin and subcutaneous bleeding. This acquired disease with severe bleeding is uncommon in adults and provides a diagnostic dilemma with normal coagulation tests at presentation. We describe two patients who presented to our institution with uncommon patterns of bleeding and were diagnosed to have FXIII deficiency. These case vignettes highlight the real-world problems associated with the diagnosis and management of FXIII deficiency.

Natl Med J India 2021;**34:**276–8

INTRODUCTION

Factor XIII (FXIII) deficiency is a rare bleeding disorder with an incidence of 1–2 per million. It is characterized by a high frequency of umbilical stump bleeding, followed by skin, subcutaneous and muscle bleeding as other common manifestations.[1] It is often overlooked as a cause of serious bleeding, and usually associated with a delay in diagnosis.[2] Numerous reports have implicated FXIII deficiency in the setting of serious bleeding, resulting in increased financial burden and reduced quality of life (QoL). The rarity of the disease and the absence of aetiology in a majority of patients with acquired deficiency may explain the high rate of delayed diagnosis. We describe two adults who presented with unusual manifestations of FXIII deficiency and real-life challenges in reaching a diagnosis, along with a summary of diagnosis and treatment of such patients.

THE CASES

Patient 1

Mrs A, a 76-year-old woman presented with swelling and discolouration over her left axilla for a week. She was evaluated elsewhere and found to have a large area of ecchymosis over the axilla and medial aspect of the left arm. An ultrasound showed features of subcutaneous haematoma, along with reduced flow in the axillary vein, leading to the diagnosis of deep venous thrombosis. She was started on enoxaparin but in view of worsening pain and swelling presented to us for further management. Examination revealed a 20 cm × 18 cm ecchymotic area over the axilla and arm, with local fullness. An ultrasound showed subcutaneous collection with no evidence of deep venous thrombosis. Enoxaparin was stopped and she was evaluated for any underlying bleeding disorder. She had a history of two deliveries in the past and a hip replacement surgery 1 year ago without any abnormal bleeding. Investigations revealed a normal platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen. A thromboelastogram showed accelerated clot lysis at 8.2%. A FXIII assay revealed undetectable FXIII activity, indicating severe deficiency. In view of her age, she was worked up for co-existent malignancy and autoimmune disorders, both of which were negative. She was given cryoprecipitates at a dose of 1 unit per 10 kg body weight, following which her bleeding stopped.

Patient 2

Mr K, a 50-year-old man presented with a history of sudden onset abdominal pain 1 year before admission. On evaluation elsewhere, he was found to have a peri-splenic haematoma with active bleeding. He underwent an emergency CT angiography, followed by splenic artery embolization. No further evaluation was done and he was subsequently well for 6 months. He presented again with discolouration over the right axilla, associated with pain. Initial examination revealed the presence of ecchymosis, and an ultrasound showed a subcutaneous haematoma. A CT angiography revealed active bleeding from a branch of the axillary artery, which was embolized by intervention radiology. Investigations revealed a normal platelet count, PT, aPTT and fibrinogen. A FXIII assay was advised, but he left against medical advice and was on follow-up locally. After 3 months, he presented to us with sudden onset of headache, vomiting and giddiness. A CT scan of the brain revealed a large cerebellar haematoma with peri-lesional oedema. A repeat work-up revealed the presence of low FXIII activity, for which he was given cryoprecipitates. He had no further episodes of bleeding and was well after that.

DISCUSSION

FXIII is a pro-enzyme that facilitates cross-linking of fibrin chains in a blood clot. Although it is known for its haemostatic effect, it has been found to have several physiological roles in angiogenesis, wound healing and maintenance of normal pregnancy.[3] It is a hetero-tetramer, consisting of two A-subunits and two B-subunits.[4] The A-subunits are produced in haematopoietic cells and can be found in platelets, monocytes and macrophages. On the other hand, the B-domain is produced in the liver and helps to stabilize the structure of FXIII. The A-domains contain the catalytic component, which is normally concealed by an activation peptide, precluding access to the substrate.[5] During haemostasis, cleavage by thrombin leads to exposure of the active site, which then binds covalently and cross-links two fibrin chains.[6]

The cases discussed above illustrate important real-world lessons while managing patients with unexpected bleeding in the setting of FXIII deficiency.

Department of Clinical Haematology and Bone Marrow Transplantation, Dayanand Medical College, Ludhiana, Punjab, India; *suvirs@gmail.com*

[**To cite:** Singh S. Factor XIII deficiency: Lessons from two patients with unusual bleeding. *Natl Med J India* 2021;**34:**276–8.]

FXIII deficiency with no history of bleeding needs a high index of suspicion

FXIII deficiency, a rare disease, has an incidence of 1–2 per million population. The most common manifestation described is umbilical stump bleeding at birth, occurring in >80% of affected patients, followed by skin and muscle bleeds.[7] FXIII deficiency may be either inherited or acquired, and more than 150 mutations leading to inherited deficiency have been described.[8] Delay in diagnosis, especially in acquired forms, appears to be the norm, with data from a tertiary centre documenting a median delay of 1.5 month before a diagnosis is reached.[2]

Both our patients had multiple encounters with other healthcare systems before contacting us. The recommended screening test for FXIII deficiency, the urea clot lysis, was not available for the first patient, necessitating a thromboelastography for further work-up. The urea clot solubility test, which has traditionally been recommended for diagnosing FXIII deficiency, has now been reported to have low sensitivity and specificity. A number of pre-analytical variables, including the choice of lysing agents (urea, acetic acid) or clot-inducing agent (thrombin, calcium) are also known to significantly affect the test performance.[9] The current consensus recommends FXIII activity assay or molecular characterization for a definitive diagnosis of FXIII deficiency and advises against the use of urea clot lysis.[9] Even after initial suspicion, a universal algorithm cannot be recommended, as most mutations noted with congenital FXIII deficiency are endemic and vary across geographical locations.[10] Each laboratory must therefore have its own algorithm based on the common endemic genetic markers.[11] Moreover, the molecular laboratory evaluating the FXIII gene mutations should remember that FXIII has multiple polymorphic variants consisting of over 25 haplotypes.[12]

Acquired forms of FXIII deficiency

In an adult patient with unexplained skin, soft tissue or muscle bleeding, acquired haemophilia is often the first suspicion, with acquired haemophilia A being the most common.[13] Acquired deficiency of FXIII was first described in the 1970s by Lorand, who classified inhibition of FXIII based on the underlying mechanism.[14] Since then, acquired FXIII deficiency has been reported to occur in immune- or non-immune-mediated settings. Immune-mediated FXIII inhibition is described in the setting of malignancies, autoimmune diseases or drugs. These patients usually present with major bleeding manifestations. On the other hand, non-immune mechanisms such as increased consumption or reduced synthesis are less likely to lead to major abnormal bleeding.[15] However, it has been seen that over 50% of acquired FXIII deficiency may be idiopathic, with no specific underlying cause being identified.[16]

Our patients probably represent an acquired pathology, as both had a history of multiple haemostatic challenges without any abnormal bleeding. Considering their age, work-up for malignancy was particularly important and was negative for both patients. Both patients are being regularly followed up for development of any malignancy or autoimmune disease.

Contribution of FXIII to arterial and stromal function is being identified, and may explain the pattern of bleeding with FXIII deficiency

FXIII has multiple well-defined roles beyond haemostasis. The association of poor wound healing with FXIII deficiency was noted in the first patient with FXIII deficiency ever described.[17] Knock-out mice for FXIII genes display impaired wound healing and abnormal scar formation.[18] It has since been elucidated that FXIII acts on a number of substrates vital to stromal function, including thrombospondin, von Willebrand factor (vWF), vitronectin and osteopontin.[19] These proteins are essential for the maintenance of stromal structure, wound healing and attachment of cells to connective tissue matrix. Initiation of wound healing by migration of fibroblasts to site of injury is also mediated by FXIII.[20] A similar effect is noted on endothelial cell function, proliferation and survival.[21] These pleiotropic effects of FXIII may explain the unique patterns of bleeding in FXIII and FIX deficiencies. FXIII deficiency perhaps impairs matrix integrity, leading to skin and connective tissue bleeding. This is in keeping with roles of FXIII in stromal function, angiogenesis and vascular permeability.[22,23] Presentation of FXIII late in life with major arterial bleeding continues to be uncommon and may be related to the effects of FXIII on arterial function. Certain FXIII polymorphisms reduce the risk for coronary artery disease with a concurrent rise in the risk for intracerebral bleeding, indicating a fine balance of FXIII function, which may be tipped in either direction.[24]

FXIII deficiency, though rare, is a healthcare burden

FXIII deficiency is associated with increased financial burden and reduced QoL. Registry data indicate that congenital FXIII deficiency is associated with relatively high rates of severe bleeding, seen in >48% of patients. Intracerebral bleeding, seen in >30% of patients, is the leading cause of mortality in this cohort.[25] The data on QoL or cost of treatment of FXIII deficiency are sparse, but both the above factors putatively lead to impaired QoL.[26] Patients with serious or life-threatening bleeding require prophylactic therapy to prevent further such episodes. FXIII concentrates, both plasma-derived and recombinant, have been available for the past few years. Plasma-derived FXIII (pdFXIII) has been shown to be effective in reducing bleeding rates.[27] Recombinant FXIII was made available in 2014 but remains in sparse use due to prohibitive costs.[28] Both these can be administered every 3–4 weeks, owing to the long half-life of FXIII.[29] However, cost and availability continue to be a concern, and most patients on prophylactic treatment have to depend on cryoprecipitate or plasma infusions. Our patients have done well on cryoprecipitate infusions every 4 weeks. The cost of extended cryoprecipitate prophylaxis has to be kept in mind, with the cost reaching upwards of US$ 100 for each infusion for a 60 kg adult in a non-subsidized setting. This is in addition to the baseline risk of infection and adverse effects associated with each transfusion.

Conclusion

FXIII is an under-recognized cause of serious or life-threatening bleeding, especially in adult patients with no history of bleeding. Considering that a majority of patients with acquired FXIII deficiency may not have an immediately recognizable aetiology, a high index of suspicion is required for diagnosis. This is more so in the setting of unusual sites of bleeding such as skin, connective tissue or other major arterial networks. Major arterial bleeding appears to be increasingly described in this setting, possibly owing to the pleiotropic effects of FXIII. More importantly, urea clot lysis should best be used as a screening tool and should be replaced by FXIII activity assay and molecular testing wherever possible.

Conflicts of interest. None declared

REFERENCES

1 Odame JE, Chan AK, Wu JK, Breakey VR. Factor XIII deficiency management: A review of the literature. *Blood Coagul Fibrinolysis* 2014;**25:**199–205.
2 Arokszállási Á, Ilonczai P, Rázsó K, Oláh Z, Bereczky Z, Boda Z, *et al*. Acquired haemophilia: An often overlooked cause of bleeding. Experience from a Hungarian tertiary care centre. *Blood Coagul Fibrinolysis* 2012;**23:**584–9.
3 Dorgalaleh A, Rashidpanah J. Blood coagulation factor XIII and factor XIII deficiency. *Blood Rev* 2016;**30:**461–75.
4 Carrell NA, Erickson HP, McDonagh J. Electron microscopy and hydrodynamic properties of factor XIII subunits. *J Biol Chem* 1989;**264:**551–6.
5 Muszbek L, Bagoly Z, Cairo A, Peyvandi F. Novel aspects of factor XIII deficiency. *Curr Opin Hematol* 2011;**18:**366–72.
6 Inbal A, Dardik R. Role of coagulation factor XIII (FXIII) in angiogenesis and tissue repair. *Pathophysiol Haemost Thromb* 2006;**35:**162–5.
7 Duckert F. The fibrin stabilizing factor, factor XIII. *Blut* 1973;**26:**177–9.
8 Muszbek L, Katona É. Diagnosis and management of congenital and acquired FXIII deficiencies. *Semin Thromb Hemost* 2016;**42:**429–39.
9 Dorgalaleh A, Tabibian S, Hosseini S, Shamsizadeh M. Guidelines for laboratory diagnosis of factor XIII deficiency. *Blood Coagul Fibrinolysis* 2016;**27:**361–4.
10 Dorgalaleh A, Naderi M, Hosseini MS, Alizadeh S, Hosseini S, Tabibian S, *et al*. (eds). *Factor XIII deficiency in Iran: A comprehensive review of the literature. Seminars in thrombosis and hemostasis*. London:Thieme Medical Publishers; 2015.
11 Ivaskevicius V, Seitz R, Kohler HP, Schroeder V, Muszbek L, Ariens RA, *et al*. International registry on factor XIII deficiency: A basis formed mostly on European data. *Thromb Haemost* 2007;**97:**914–21.
12 Suzuki K, Henke J, Iwata M, Henke L, Tsuji H, Fukunaga T, *et al*. Novel polymorphisms and haplotypes in the human coagulation factor XIII A-subunit gene. *Hum Genet* 1996;**98:**393–5.
13 Franchini M, Vaglio S, Marano G, Mengoli C, Gentili S, Pupella S, *et al*. Acquired hemophilia A: A review of recent data and new therapeutic options. *Hematology* 2017;**22:**514–20.
14 Lorand L. Hemorrhagic disorders of fibrin stabilization. In: *Hemostasis: Biochemistry, physiology and pathology.* London:John Wiley & Sons; 1977:405–23.
15 Yan MTS, Rydz N, Goodyear D, Sholzberg M. Acquired factor XIII deficiency: A review. *Transfus Apher Sci* 2018;**57:**724–30.
16 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.
17 Duckert F, Jung E, Shmerling DH. A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilizing factor deficiency. *Thromb Diath Haemorrh* 1960;**5:**179–86.
18 Inbal A, Lubetsky A, Krapp T, Castel D, Shaish A, Dickneitte G, *et al*. Impaired wound healing in factor XIII deficient mice. *Thromb Haemost* 2005;**94:**432–7.
19 Corbett SA, Lee L, Wilson CL, Schwarzbauer JE. Covalent cross-linking of fibronectin to fibrin is required for maximal cell adhesion to a fibronectin–fibrin matrix. *J Biol Chem* 1997;**272:**24999–5005.
20 Dardik R, Krapp T, Rosenthal E, Loscalzo J, Inbal A. Effect of FXIII on monocyte and fibroblast function. *Cell Physiol Biochem* 2007;**19:**113–20.
21 Muszbek L, Bereczky Z, Bagoly Z, Komáromi I, Katona É. Factor XIII: A coagulation factor with multiple plasmatic and cellular functions. *Physiol Rev* 2011;**91:**931–72.
22 Birnbaum J, Hein OV, Lührs C, Rückbeil O, Spies C, Ziemer S, *et al*. Effects of coagulation factor XIII on intestinal functional capillary density, leukocyte adherence and mesenteric plasma extravasation in experimental endotoxemia. *Critical Care* 2006;**10:**R29.
23 Nagy JA, Dvorak AM, Dvorak HF. Vascular hyperpermeability, angiogenesis, and stroma generation. *Cold Spring Harb Perspect Med* 2012;**2:**a006544.
24 Gemmati D, Serino ML, Ongaro A, Tognazzo S, Moratelli S, Resca R, *et al*. A common mutation in the gene for coagulation factor XIII-A (VAL34Leu): A risk factor for primary intracerebral hemorrhage is protective against atherothrombotic diseases. *Am J Hematol* 2001;**67:**183–8.
25 de Jager T, Pericleous L, Kokot-Kierepa M, Naderi M, Karimi M. The burden and management of FXIII deficiency. *Haemophilia* 2014;**20:**733–40.
26 Lak M, Peyvandi F, Ali Sharifian A, Karimi K, Mannucci PM. Pattern of symptoms in 93 Iranian patients with severe factor XIII deficiency. *J Thromb Haemost* 2003;**1:**1852–3.
27 Ashley C, Chang E, Davis J, Mangione A, Frame V, Nugent DJ. Efficacy and safety of prophylactic treatment with plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. *Haemophilia* 2015;**21:**102–8.
28 Dorey E. First recombinant factor XIII approved. *Nat Biotechnol* 2014;**32:**210.
29 Inbal A, Oldenburg J, Carcao M, Rosholm A, Tehranchi R, Nugent D. Recombinant factor XIII: A safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012;**119:**5111–17.