sciendo

CASE STUDY

Management of a patient with factor X deficiency with FEIBA: a case report

Luish Borboruah, Anupam Dutta

Hereditary factor X (FX) deficiency is a rare autosomal recessive disorder that increases bleeding tendencies, ranging from epistaxis to intracranial haemorrhage (ICH), which can be life-threatening. Single factor concentrates are recommended for treating rare bleeding disorders; however, in India most people with FX deficiency are treated with fresh frozen plasma (FFP). We report a case of FX deficiency in a child with a history of intracranial bleeding who was found to have a novel mutation in the F10 gene. Although managed with weekly prophylactic FFP infusions, he continued to experience regular bleeding including two further instances of ICH. Other therapeutic options were unavailable or unaffordable. When the Indian Government added FEIBA to the essential drug list, a decision was made to try FEIBA prophylaxis to better manage his bleeding. In 2019, he was started on a weekly dose of FEIBA, 500 IU (20 IU/kg and his prophylactic FFP transfusion regimen was stopped. His bleeding episodes started to reduce after two months of starting FEIBA prophylaxis. Over the last three years he has had only four minor bleeding episodes and has remained completely free of major bleeding. He is now able to receive home-based therapy and his prognosis can be considered to be improved. FEIBA may be a useful medicinal therapy for FX-deficient patients who suffer severe haemorrhagic episodes in countries where plasma-derived factor X (pdFX) is not available.

LUISH BORBORUAH
Assam Medical College and Hospital, Dibrugarh, India.
Email: luishborboruah128@gmail.com

ANUPAM DUTTA
Assam Medical College and Hospital, Dibrugarh, India

©Pranabnlp / CC BY-SA-4.0

A report on a case of factor X deficiency from Assam Medical College and Hospital indicates that FEIBA prophylaxis may be a useful therapy in settings where plasma-derived factor X concentrate (pdFX) is not available

Keywords: *Factor X deficiency, Fresh frozen plasma (FFP), FEIBA, Intracranial haemorrhage, Case report*

Factor X (FX) is a vitamin K-dependent plasma glycoprotein that plays an important role in the blood coagulation cascade. Congenital FX deficiency is a rare autosomal recessive bleeding disorder [1]. The tendency of bleeding can be once or recurrent and can vary in degree from mild to severe based on the level of the FX in the blood. The most common symptoms are epistaxis, gingival bleeding, and menorrhagia [2,3]. Infants and neonates with severe FX deficiency are at high risk of intracranial haemorrhage (ICH) [4].

FX deficiency represents ~10% of all rare bleeding disorders [5]. As with other rare bleeding disorders, FX deficiency occurs more commonly within communities who practice consanguineous marriage. FX deficiency is classified as either type I, with reduced factor X activity and reduced factor X antigen, or type II, distinguished by reduced factor X activity but normal factor X antigen [6].

The World Federation of Hemophilia (WFH) recorded 67 cases of FX in India in its 2021 Annual Global Survey [7]. Cases of FX deficiency in India have been reported in the literature by Shah et al., who reported on eight cases in 2008 [8], and other cases have been reported by Sinha et al. [9] and Chatterjee et al. [10]. In all previously reported cases in India, the patients have been managed with fresh frozen plasma (FFP) transfusion, which is the primary treatment for FX deficiency in our country. Other therapeutic options for FX deficiency include prothrombin complex concentrates (PCCs), dual-factor IX/X therapy, and human plasma-derived factor X concentrate (pdFX) [11]. Single factor concentrates are recommended for treating rare bleeding disorders where possible [12].

Whereas prothrombin complex concentrates (PCCs) are essentially used to replace a deficit in clotting factors, FEIBA (factor eight inhibitor bypassing activity) is designed to directly trigger the clotting process. FEIBA can facilitate thrombin generation and contains the proenzymes of the prothrombin complex factors, prothrombin, FVII, FIX and FX, which play a major role in clotting of blood [13]. Factor VIIa present in FEIBA forms a complex with tissue factor and calcium which converts endogenous and FEIBA contained factor X to Xa. Endogenous and FEIBA contained factor Xa act as part of the prothrombinase complex which then converts endogenous and FEIBA contained prothrombin to thrombin. It is useful in patients who have developed an inhibitor against factor VIII and also in patients with FX deficiency [5].

Here, we present a rare case of FX deficiency with a history of intracranial bleeding who is currently under successful prophylactic therapy with FEIBA.

CASE REPORT

Our patient, who was born of a nonconsanguineous marriage and without a family history of any bleeding disorder, first presented with fever, vomiting and seizures in 2010 at the age of 4 months. His reports showed anaemia (Hb=10 g/dl) and leucocytosis with features of sepsis. His liver and renal function tests were normal. After stabilisation cerebrospinal fluid (CSF) analysis was undertaken, which revealed pyogenic meningitis. A CT brain scan revealed left sided subdural haemorrhage with midline shift, and prolonged PT (36.4s; reference range is 12.5s) and aPTT (99.3s; reference range: 27.6-42.4s) was noted. Considering it to be a case of bacterial meningitis with sepsis and sepsis-induced coagulopathy, the child was treated with intravenous antibiotics, FFP transfusion and other supportive care.

One month after discharge, the child again presented with seizures and raised intracranial tension without any history of fever or trauma. His CT scan showed chronic subdural haematoma with rebleeding. Thereby a panel of investigation was planned, which showed haemoglobin (11.1 g/dl), total leukocyte count (12,400/ cu. Mm) and normal platelet count (1,24,000/ cu. Mm). This time he was evaluated for a possible coagulation disorder. The resulting coagulation profile is shown in Table 1 and factor assay results in Table 2.

Based on the reports the child was diagnosed with severe FX deficiency. Genetic analysis was undertaken to confirm the diagnosis and to establish the mutation in the F10 gene. This revealed a novel single nucleotide change T>G (c.336) at codon 112 of the F10 gene (Figure 1). Genetic analysis of both parents and two elder sisters revealed that they were all heterozygous for the same mutation.

A treatment regimen was started whereby the child received a weekly prophylactic FFP infusion, and this continued for next 9 years. Despite this he experienced repeated episodes of joint bleed, gum bleeding and epistaxis at intervals ranging between 10-14 days, which impaired his daily activities. During this time he also

Table 1. Coagulation profile results

TEST	PATIENT VALUE	REFERENCE
Prothrombin time	52.7s	12.5s
aPTT	84.9s	27.6-42.4s
INR	4.80	
Thrombin time	13.5s	12.0-16.0s

INR: International normalised ratio

Table 2. Factor assay results

TEST	PATIENT VALUE	REFERENCE
Factor VIII	173.6%	50-150%
Factor X	<1%	50-150%
Fibrinogen	231.5mg/dl	150-450mg/dl
Ristocetin co factor assay	89%	50-175%

Figure 1: Genetic analysis
Procedure and results of F10 gene testing

Sample type:
- Blood sample received in EDTA anticoagulant vacutainers
- DNA extracted by commercial kit (Gentra Puregene blood kit, Qiagen Gmbh)

Gene tested:
F10 emsembl reference sequence: ENST00000375559

Method:
Direct DNA sequencing

Procedure:
- Multiplex PCR of F10 promoter, 8 exons (including 20-40 nucleotides flanking the exon) and poly adenylation site
- Bidirectional sequencing of the amplicons

Results:

	PCR	DNA SEQUENCING
Patient	Exon 4	c.336T>G p.cys112Trp(Homozygous)
Mother	Exon 4	c.336T>G p.cys112Trp(Heterozygous)
Father	Exon 4	c.336T>G p.cys112Trp(Heterozygous)

Comment:
The F10 gene mutation is a novel single nucleotide change T>G (c.336) at codon 112 of the F10 gene. This mutation predicts an amino acid change, Cys>Trp at codon 112 in the EGF domain of F10.

Interpretation: The disease affecting the patient is caused by a missense mutation (p.cys112Trp) in the F10 gene

developed two further episodes of intracranial bleeding, in 2013 and in 2015, which were managed with FFP transfusion.

In 2019, after FEIBA was added to the National List of Essential Medicines by the Indian Government, a decision was made to try FEIBA prophylaxis in the hope of better managing the child's bleeding. He was started on a weekly dose of FEIBA, 500 IU (20 IU/kg) and his prophylactic FFP transfusion regimen was stopped. The child was initially monitored on a weekly basis for six months. After two months of starting FEIBA prophylaxis his bleeding episodes started to reduce. After six months, the frequency of his monitoring visits was reduced to every two weeks, and after a further six months to monthly clinic visits. He has not experienced allergic reaction following administration of the product.

The efficacy of the treatment Is supported by the fact that in the last three years, since starting FEIBA prophylaxis, the child has had only four minor bleeding episodes and has remained completely free of any major bleeding episodes. His last recorded bleeding episode was cutaneous bruising in 2020. His parents have been trained to administer FEIBA and he is now able to receive home-based therapy. A timeline overview of the child's case is shown in Figure 2.

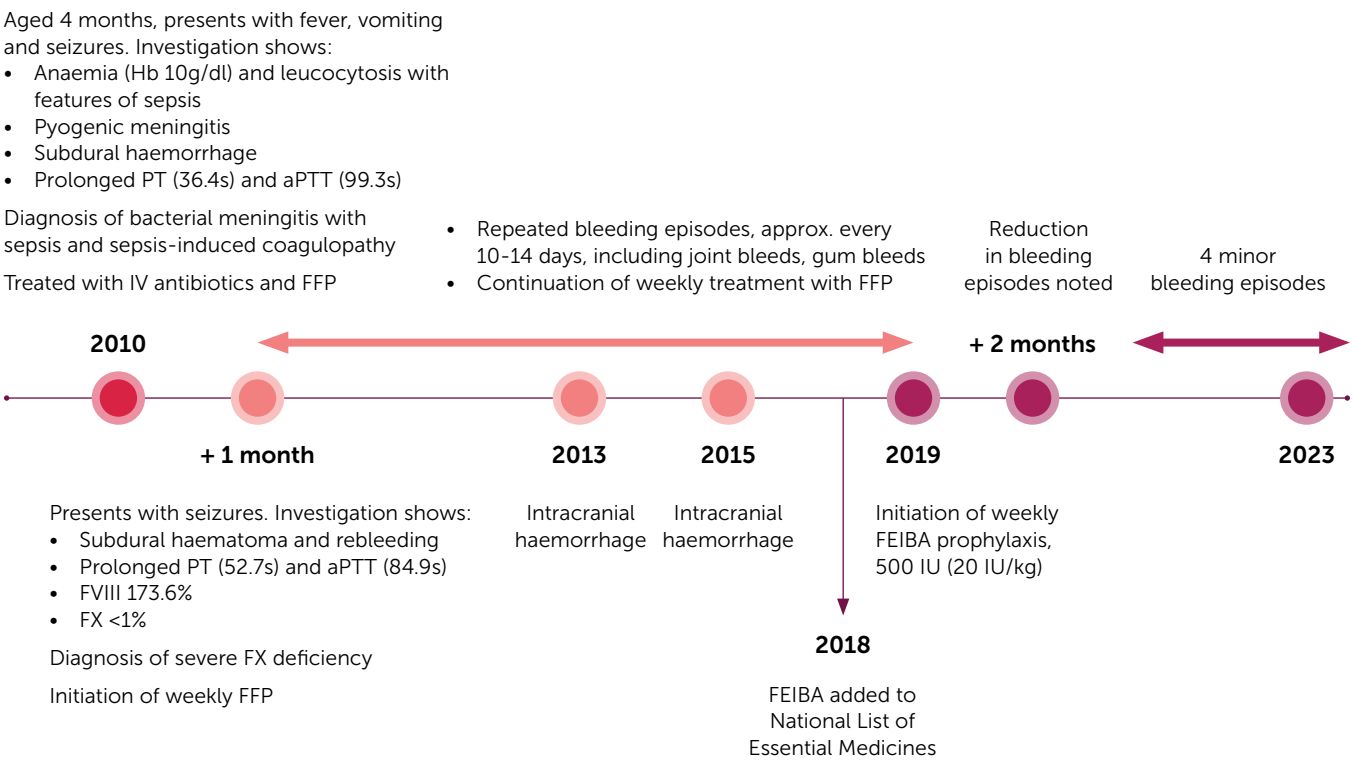
Our treatment plan is for the child to continue to receive FEIBA prophylactically unless, on review, a non-response to FEIBA develops or another better, reliable and affordable choice becomes available. Based on his clinical status over the last three years, his prognosis can be considered to be improved since starting FEIBA prophylaxis.

DISCUSSION

Decreasing FX coagulant (FX:C) activity is associated with increasing severity of bleeding in FX deficiency [2,12,14]. A study by the European Network of Rare Bleeding Disorders (EN-RBD) reported that FX:C levels at which patients were asymptomatic or had grade 1, 2, or 3 bleeding were 56, 40, 25, respectively [15]. Based on data from the EN-RBD registry, and in this study, patients with factor X activity levels of >40, 10–40 and <10 IU/dL were classified as being largely asymptomatic, suffering minor spontaneous or triggered bleeding, or having a high risk of major spontaneous bleeding, respectively [16].

In the case reported here, the child had severe FX deficiency that manifested with intracranial haemorrhage (ICH) and a FX level <1%. Genetic testing revealed a novel missense mutation which, to our knowledge, has not been recorded in other available published literature. Shinohara et al. [17] report 105 mutations of the F10 gene; 82 are missense mutations (representing 78% of all mutations), 14 deletions (3 gross deletions + 11 microdeletions), 6 splice site mutations, 2 nonsense mutations, and 1 mutation in the 50 flanking region.

Figure 2. Timeline overview from first presentation to date



Most gene mutations are located in exon 8; the number of mutations located in each exon is proportional to the length of the exon itself, indicating the absence of a hot-spot region in F10 [18,19]. Gene deletions result in premature termination and thus the loss of the FX catalytic domain, whilst missense mutations may also affect phospholipid binding, activation, secretion, or even FX synthesis [6]. These mutant FXs have been named according to the proband's origin, for example, factor X Prower [19], factor X Stuart [20], factor X San Antonio I [21] and factor X Friuli [22].

Following diagnosis, the child in our case went on to have further episodes of intracranial bleeding, as well as repeated joint bleeds, gum bleeds and epistaxis, despite regular treatment with plasma replacement therapy. Multiple episodes of ICH in infants with FX deficiency have been reported elsewhere. Ermis et al. reported a case of infants who developed ICH twice, with prophylactic plasma replacement therapy proving ineffective [23]. Sandler et al. reported an infant who experienced three episodes of ICH in first 6 months of life, but where no further bleeding occurred after the initiation of secondary prophylaxis [24]. El Kalla et al. also reported two cases who developed intracranial haemorrhage twice [25]. In the first case, ICH developed at 3 days old and secondary prophylaxis was not started until a second ICH developed at age of 4 months. In the second case ICH developed at age of 3 days and a second episode developed despite regular replacement.

In the past, bleeding episodes in people with coagulation disorders were treated with whole blood replacement and later FFP products. More recently, with development of knowledge about rare coagulation factor disorders and advances in technological abilities, a range of replacement therapies have been developed. Current therapeutic options for FX deficiency include FFP, cryoprecipitate, prothrombin complex concentrates (PCCs), dual-factor IX/X therapy, and human plasma-derived factor X concentrate (pdFX) [11]. Receiving regular FFP did not prevent bleeding in the case reported here; however, it was not possible to consider these other therapeutic options as they were either unavailable or unaffordable.

In a study conducted by Shim et al. FEIBA was introduced as a prophylactic therapy in a 22-month-old child with past history of recurrent intracranial haemorrhage at 74 IU/kg once weekly dose for 11 months. During that period the child developed 43 episodes of minor bleeding, all which occurred following trauma; however no episodes of intracranial haemorrhage were noted [26]. In 2018, the Indian Government added FEIBA to the National List of Essential Medicines. Prior to this, it was not possible to consider it as a potential treatment option for the child

in our case as his parents could not afford the high cost. However, since starting FEIBA prophylaxis, it has been seen to be similarly effective.

Since FEIBA is produced from human plasma there is a risk that it may carry infectious agents, such as viruses and variant Creutzfeldt-Jakob disease (vCJD). To minimise this risk, plasma donors are now screened, and the manufacturing process involves the inactivation and removal of certain viruses. There is still a risk that human pathogenic agents may be transmitted, and hence it remains a major issue to be addressed. In our case the child was vaccinated against hepatitis B; however, he has not been vaccinated against hepatitis A.

CONCLUSION

Although less common than Factor VIII and Factor IX deficiency, Factor X deficiency should also be considered in a young patient with deranged bleeding profile. In these patients, early diagnosis and effective replacement therapy is crucial for the prevention of central nervous system bleeding. In our case, the primary therapeutic option available, FFP, was not effective in managing the child's bleeding. However, we have found that the prophylactic use of FEIBA is helping to manage the child's bleeding and has, as a result, dramatically improved his quality of life. FEIBA may be a useful medicinal therapy for FX-deficient patients who suffer severe haemorrhagic episodes in countries where plasma-derived factor X concentrate (pdFX) is not available.

ACKNOWLEDGEMENTS

The authors have advised no interests that might be perceived as posing a conflict or bias.

Informed consent has been obtained from the parents of the child reported in this paper.

ORCID

Luish Borboruah https://orcid.org/0009-0006-8266-6691
Anupam Dutta https://orcid.org/0000-0001-9520-5196

REFERENCES

1. Peyvandi F, Mannucci PM, Lak M, et al. Congenital factor X deficiency: spectrum of bleeding symptoms in 32 Iranian patients. *Br J Haematol* 1998; 102: 626-628. doi: 10.1046/j.1365-2141.1998.00806.x.
2. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood* 2015; 125: 2052-2061. doi: 10.1182/blood-2014-08-532820.
3. Al-Mouqdad M, Abdelrahim A, Kahlon BMM, Almahmoud L, Asfour S. A successful treatment of infant who had two significant intracranial hemorrhage with factor X replacement: case report. *Neonat Pediatr Med* 2018; 4: 163. doi: 10.4172/2572-4983.1000163.
4. Escobar MA. Advances in the treatment of inherited coagulation disorders. *Haemophilia* 2013; 19: 648-659. doi: 10.1111/hae.12137.
5. Menegatti M, Peyvandi F. Factor X deficiency. *Semin Thromb Hemost* 2009; 35: 407-415. doi: 10.1055/s-0029-1225763.
6. Powell JS, Rodgers GM. Inherited coagulation disorders. In: Greer JP, Arber DA, Glader B, et al. (eds.). *Wintrobe's Clinical Hematology*. 13th edn. 2014. Philadelphia: Lippincott Williams & Wilkins.1143-1185.
7. World Federation of Hemophilia. Report on the Annual Global Survey 2021. October 2022. Available from *https://www1.wfh.org/publications/files/pdf-2324.pdf* (accessed 10 June 2023).
8. Shah NM, Patel AP. An analysis of 8 cases of factor X deficiency. *Indian J Hematol Blood Transfus* 2008; 24 (1): 23-25. doi: 10.1007/s12288-008-0018-7.
9. Sinha S, Barik S. Factor X deficiency: a rare case of inherited coagulation disorder presenting as hemarthrosis. *Int J Med Res Rev* 2014; 2(3): 253-255. doi:10.17511/ijmrr.2014.i03.14.
10. Chatterjee T, Philip J, Nair V, et al. Inherited factor X (Stuart-Prower factor) deficiency and its management. *Med J Armed Forces India* 2015; 71 (suppl 1): S184-S186. doi: 10.1016/j.mjafi.2014.01.007.
11. Peyvandi F, Auerswald G, Austin SK, et al. Diagnosis, therapeutic advances, and key recommendations for the management of factor X deficiency. *Blood Rev* 2021; 50: 100833. doi: 10.1016/j.blre.2021.100833.
12. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol* 2014; 167: 304-26. doi: 10.1111/bjh.13058.
13. Turecek PL, Váradi K, Gritsch H, Schwarz HP. FEIBA: mode of action. *Haemophilia* 2004; 10 Suppl 2: 3-9. doi: 10.1111/j.1365-2516.2004.00934.x.
14. Bolton-Maggs PH, Perry DJ, Chalmers EA, et al. The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004; 10: 593-628. doi: 10.1111/j.1365-2516.2004.00944.x.
15. Peyvandi F, Palla R, Menegatti M, 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. doi: 10.1111/j.1538-7836.2012.04653.x.
16. 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: 1938-43. doi: 10.1111/j.1538-7836.2012.04844.x.
17. Shinohara K, Adachi M, Matsui K, et al. A case of factor X (FX) deficiency due to novel mutation V196M, FX Hofu. *Int J Hematol* 2008; 87(3): 256-259. doi: 10.1007/s12185-008-0035-1.
18. Peyvandi F, Menegatti M, Santagostino E, et al. Gene mutations and three-dimensional structural analysis in 13 families with severe factor X deficiency. *Br J Haematol* 2002; 117: 685-692. doi: 10.1046/j.1365-2141.2002.03486.x.
19. Telfer TP, Denson KW, Wright DR. A 'new' coagulation defect. *Br J Haematol* 1956; 2(3): 308-316. doi: 10.1111/j.1365-2141-1956.tb06703.x.

20. Hougie C, Barrow EM, Graham JB. Stuart clotting defect. I. Segregation of an hereditary hemorrhagic state from the heterogeneous group heretofore called stable factor (SPCA, proconvertin, factor VII) deficiency. *J Clin Invest* 1957; 36: 485-496. doi: 10.1172/JCI103446.
21. Redely SV, Zhou ZQ, Rao KJ, Scott JP, Watzke H, High KA, Jagadeeswaran P. Molecular characterization of human factor XSan.Antonio. *Blood* 1989; 74(5): 1486-90. doi: 10.1182/blood.V74.5.1486.1486.
22. James HL, Girolami A, Fair DS. Molecular defect in coagulation factor XFriuli results from a substitution of serine for proline at position 343. *Blood* 1991; 77: 317-323. doi: 10.1182/blood.V77.2.317.317.
23. Ermis B, Ors R, Tastekin A, Orhan F. Severe congenital factor X deficiency with intracranial bleeding in two siblings. *Brain Dev* 2004; 6: 137-138. doi: 10.1016/S0387-7604(03)00119-0.
24. Sandler E, Gross S. Prevention of recurrent intracranial hemorrhage in a factor X-deficient infant. *Am J Pediatr Hematol Oncol* 1992; 14: 163-165. doi: 10.1097/00043426-199205000-00012.
25. el Kalla S, Menon NS. Neonatal congenital factor X deficiency. *Pediatr Hematol Oncol* 1991; 8: 347-354. doi: 10.3109/08880019109028808.
26. Shim YJ, Won DI. Pharmacokinetics and prophylactic use of FEIBA ® in a child with severe congenital factor X deficiency and recurrent spontaneous intracranial haemorrhage: a case report. *Haemophilia* 2013; 19(6): e364–7. doi: 10.1111/hae.12245.

HOW TO CITE THIS ARTICLE:
Borboruah L, Dutta A. Management of a patient with factor X deficiency with FEIBA: a case report. *J Haem Pract* 2023; 10(1): 68-73. *https://doi.org/10.2478/jhp-2023-0012*