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COMMENTARY

Factor X deficiency: a comment on two recent case studies

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Hereditary factor X deficiency (HFXD) is a rare genetic bleeding disorder, affecting approximately 1 in 1,000,000 individuals globally, and resulting in abnormally low activity of clotting factor X (FX). Diagnosis may occur early in life, particularly in patients with a family history of the disorder or severe deficiency, or later in life for those with mild-moderate deficiency. Regardless of age at diagnosis, this disorder can significantly impact the lives of patients, as well as those of caregivers and/or family members. Alongside a wide historical array of HFXD treatments, including supportive care with blood transfusions, FX replacement with fresh frozen plasma or prothrombin complex concentrates, specific replacement has been made possible with the isolation and concentration of human plasma-derived FX for therapeutic use, offering the potential for a streamlined prophylactic regimen and improved quality of life and wellbeing. Two recent case studies describe the diagnosis and management of children with HFXD in India and the Philippines, both of whom were diagnosed in infancy following severe bleeding episodes. They share important similarities but highlight key differences in the experience of diagnosis and management of HFXD. Together they illustrate the lack of a specific target population subgroup for this rare but serious bleeding disorders, and the importance of checking FX levels (among other clotting factors) when prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged.

Keywords: *Factor X deficiency; Diagnosis; Replacement therapy; Case report*

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THIS COMMENTARY RELATES TO THE FOLLOWING PAPERS:

- 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*
- Masacupan KDT, Racho AR, Del Rosario ML, Lagaya-Aranas LM. The first reported case of factor X deficiency in a Filipino child – case study. *J Haem Pract* 2023; 10(1): 90-94. *https://doi.org/10.2478/jhp-2023-0015*

Hereditary factor X deficiency (HFXD) is a rare genetic bleeding disorder, affecting approximately 1 in 1,000,000 individuals globally, and resulting in abnormally low activity of clotting factor X (FX), an essential component of the coagulation system required to prevent haemorrhage resulting from vascular damage [1-5]. Compared to individuals with normal FX activity, FX-deficient patients are at risk of significant and severe bleeding, manifesting as spontaneous umbilical cord stump haemorrhage or intracranial haemorrhage early in life, and either spontaneous or traumatic bruising, mucosal bleeds (epistaxis, oral cavity, gastrointestinal tract), haemarthrosis, and/or muscle haematomas later in life [1,2,3]. The disorder affects individuals of both sexes equally. HFXD-affected females may experience menorrhagia, while pregnant females are at greater risk for pregnancy and delivery complications [2].

Diagnosis of HFXD may occur early in life, particularly in patients with a family history of the disorder or severe deficiency, as determined by bleeding phenotype or FX activity (factor activity of < 10 IU/dL), but may happen later in life for those with mild-to-moderate deficiency associated with less frequent and/or less severe bleeding episodes [2,3,6,7]. Regardless of age at diagnosis, this disorder can significantly impact the lives of patients, as well as those of their caregivers and/or other family members. Results from the recent HFXD in America survey of patients and caregivers demonstrated that people with HXFD experience below average health-related quality of life (QoL), while caregivers undertake a substantial burden associated with this disorder [8]. By gaining an understanding of the impact of this coagulation disorder on patient-reported outcomes such as QoL and wellbeing, future care of HFXD patients may be improved.

The wide historical array of HFXD treatments includes supportive care with blood transfusions, FX replacement with fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC), and adjunctive therapy with antifibrinolytic compounds (tranexamic acid or aminocaproic acid) and/ or hormone modulation. More recently, specific replacement has been made possible with the isolation and concentration of human plasma-derived FX for therapeutic use. As with other rare bleeding disorders, the availability of this single factor replacement therapy may streamline a prophylactic regimen of regular factor replacement to reduce risk of spontaneous and/ or traumatic bleeds compared to on-demand therapy following haemorrhagic events [9] – an approach associated with improved QoL and wellbeing in the HFXD in America survey [8].

Two recent case studies published in *The Journal of Haemophilia Practice* report on the diagnosis and management of children with FX deficiency. In the first, Borboruah and Dutta [10] describe the experience of a boy in India who presented with symptoms of intracranial haemorrhage at age four months and was eventually diagnosed with severe FX deficiency (<1%) associated with a novel mutation in *F10* one month later, after a second subdural haemorrhage. He was treated with weekly plasma infusions for nine years but suffered ongoing bleeding until transitioning to a regimen of weekly factor eight inhibitor bypassing agent (FEIBA) infusions, after which he has been free from bleeding episodes for three years.

In the second, Masacupan et al. [11] report the case of a boy in the Philippines who presented with bruising and umbilical stump bleeding in his first week of life and was subsequently diagnosed with severe FX deficiency at age two months, after developing subarachnoid haemorrhage at six weeks old. He is managed with plasma infusions every two days, but still suffers from intracranial bleeding.

These two case studies share important similarities, but also highlight some key differences in patient experience of diagnosis and management of HFXD. In both cases, diagnosis occurred 1-2 months following presentation with bleeding symptoms, when prolonged prothrombin time (PT) and partial thromboplastin time (PTT) were noted. The severe presentation, with intracranial bleeding in both cases, aligns with the severe deficiency. The age at diagnosis in both cases is younger than the median of four years reported in the HFXD in America study, in which most patients were diagnosed within three months of presentation and only seven percent underwent a delay of longer than 12 months between presentation and diagnosis [8]. However, in neither case was a purified FX replacement therapy available, so other replacement strategies were used.

The differences in nationality/ethnicity and consanguinity status of the parents in the two case studies demonstrate the variety of individuals affected by HXFD, despite its rarity. In the absence of available single factor replacement therapy, different approaches were taken to achieve haemostasis in these boys. Expert consensus guidelines in the US recommend single factor replacement therapy for HFXD [12] and the advantage of single factor concentrates over replacement therapy with FFP or PCC is recognised [13].

Taken together, these two case reports illustrate the lack of a specific target population subgroup for this rare but serious bleeding disorder. They also highlight the importance of checking FX levels (among those of other clotting factors in the common) when PT and PTT screening tests are both prolonged. Through ongoing research and advocacy to raise awareness of HFXD, improve diagnosis and management options, and enhance awareness and accessibility of single factor replacement products, we can increase QoL and wellbeing for people with this disorder, and reduce the burden reported by their caregivers.

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REFERENCES

1. Hermann FH, Auerswald G, Ruiz-Saez A, et al. Factor X deficiency: clinical manifestation of 102 subjects from Europe and Latin America with mutations in the factor 10 gene. *Haemophilia* 2006; 12: 479-489. doi: 10.1111/j.1365-2516.2006.01303.x.
2. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia* 2008; 14: 1176-1182. doi: 10.1111/j.1365-2516.2008.01856.x.
3. Tarantino MD. Occurrence and management of severe bleeding episodes in patients with hereditary factor X deficiency. *Haemophilia* 2021; 27(4): 531-543. doi:10.1111/hae.14223.
4. National Organization for Rare Disorders. Factor X Deficiency. Published 2018, 2023. Last updated 6 June 2023. Available from *https://rarediseases.org/rare-diseases/factor-x-deficiency/* (accessed November 2023).
5. National Bleeding Disorders Foundation. Factor X (Stuart-Prower Factor) Deficiency. Available from *https://www.hemophilia.org/bleeding-disorders-a-z/types/other-factor-deficiencies/factor-x* (accessed November 2023).
6. 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(9): 1938-1943. doi:10.1111/j.1538-7836.2012.04844.x.
7. Menegatti M, Peyvandi F. Factor X deficiency. *Semin Thromb Hemost* 2009; 35(4): 407-415. doi: 10.1055/s-0029-1225763.
8. Branchford B, Clark K, Stanford R, et al. Hereditary Factor X Deficiency in America Survey: Impact on quality of life and burden of disease in patients and caregivers. Manuscript submitted for publication.
9. Pall R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood* 2015; 125(13): 2052-2061. doi: 10.1182/blood-2014-08-532820.
10. 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. doi: 10.2478/jhp-2023-0012.
11. Masacupan KD, Racho AR, Del Rosario ML, Lagara-Aranas LM. The first reported case of factor x deficiency in a Filipino Child – case study. *J Haem Pract* 2023; 10(1): 90-94. doi: 10.2478/jhp-2023-0015.
12. National Bleeding Disorders Foundation. MASAC Document 280. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. 2023. Available from *https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system* (accessed November 2023).
13. 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.

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