Case report of recurrent bleeding in an infant with isolated prolonged prothrombin time due to congenital factor VII deficiency—a riddle solved

Mimi Ganguly¹, Saurabh Sutradhar¹, Arghya Rajbangshi¹, Amrita Pattnaik¹, Dipshikha Maiti²

Departments of ¹Paediatrics and ²Paediatric Haemato-oncology, Institute of Child Health, Kolkata, West Bengal, India

Abstract

Factor VII deficiency is a rare bleeding disorder showing an autosomal recessive pattern of inheritance. Data from our country on this particular entity is lacking. Especially the specific mutations associated with this disease are not well documented. The disease can have a wide spectrum of presentation from asymptomatic to catastrophic central nervous system or gastrointestinal system bleed. It can often present early in the neonatal period or be detected quite later in life. The genotype and phenotype correlation is also not well understood. Here, we report a case of recurrent bleeding in an infant boy who was otherwise absolutely well. His investigations had revealed isolated prolonged prothrombin time which remained uncorrected despite administration of injection vit K. Specific assay for factor VII level revealed that its value less than 1%. Sequencing of the F7 gene revealed our patient to be homozygous for mutation of promoter consensus sequence of F7 gene (-94C > T).

Keywords: Bleeding disorder, factor VII deficiency, prolonged prothrombin time (PT), vit K

Introduction

Congenital Factor VII (FVII) deficiency is said to be the commonest of the rare autosomal recessive inherited bleeding disorders. Congenital factor VII deficiency has an incidence of 1 per 3,00,000 to 5,00,000 individuals.¹ Data on incidence in India is lacking. A study from AIIMS suggests that the prevalence of factor VII deficiency among rare bleeding disorder is the highest (38.5%), reiterating results from other studies.² Congenital factor VII is characterised by a wide spectrum of bleeding severity. Some are asymptomatic while others may present with life threatening haemorrhagic episodes such as central nervous system bleeding.³ It is important to be able to predict the bleeding severity. The most severely affected group of patients are candidates for long-term prophylactic FVII replacement therapy. They account for around 10–15% of patients with FVII deficiency and usually have low to very low levels of FVII.⁴ Recent studies are investigating the mutation profile of factor VII (F7) gene. Most of the available data are from the Western population with very few studies from India.⁵ Our case documents the specific mutation in F7 gene which will be helpful in predicting clinical course of the patient in question. This will also add to the sparse literature and help in better understanding of this rare disorder.

Case Report

An 11 month boy, born of nonconsanguineous marriage had presented to our hospital with complaints of 2–3 episodes of...
epistaxis and gum bleeding intermittently for 2 months. There was no history of abortion or still birth. The child was otherwise well and did not have any previous history of bleeding. The father reportedly had episodes of epistaxis previously. But the episodes were self-limiting and was not investigated for same. There was no similar family history.

Investigations were done. CBC including the platelet counts were normal, but there was deranged prothrombin time (PT) with International normalised ratio (INR) of 8.6. Activated partial thromboplastin time (aPTT) was normal. He was treated with Inj vitamin K in standard doses, suspecting vitamin K deficiency associated bleeding (VKDB), but the child had persistent isolated prolonged PT. This led to the suspicion of factor VII deficiency. Factor VII assay revealed activity of less than 1%. Factor assays factor VIII and vWF antigen came to be normal.

The patient required repeated transfusions of fresh frozen plasma for restoration of normal INR. Parents were investigated for heterozygosity of factor VII deficiency. Sequencing of the F7 gene revealed our patient to be homozygous for mutation of promoter consensus sequence of F7 gene (‑94C > T). Both parents were confirmed to be heterozygous for the same mutation on chromosome 13.

Discussion

Primary care physicians may come across a bleeding child in the practice. When working up a case of bleeding child, platelet counts and coagulation parameters are the first step in the workup. Since the platelet count was normal, the possibility of coagulation disorder was kept. Acquired causes of coagulation disorders are more common in clinical practice as compared to congenital disorders. Among the acquired disorders, late vitamin K deficiency (VKDB) was kept as a working diagnosis in our case.\(^{[5,6]}\) Coagulation studies in VKDB is characterised by prolonged PT and APTT but APTT can be sometimes normal, especially in early cases. The prolonged PT and APTT in VKDB can be easily normalised by vitamin K administration. In our case the deranged PT wasn’t corrected by repeated vitamin K injection in standard doses. The combination of isolated prolonged PT not corrected by vitamin K injection, normal liver function and platelet count, in an otherwise well child led to the workup for congenital Factor VII deficiency. Confirmation of factor VII deficiency can then be done by performing factor VII assay. Patients with <1% normal factor VII levels typically present with severe symptoms.

More than 250 different mutations in F7 gene are known and the majority of them are missense mutations.\(^{[8]}\) The mutation (‑94C > T) in our patient has been described before and is associated with severe bleeding manifestations. The severe clinical phenotype observed in the patients carrying these mutations can be explained by reduced binding efficacy of the transcription factors for the F7 promoter.\(^{[9]}\) This highlights the importance of mutation profiling as it would help predict the clinical severity probably before the occurrence of life-threatening bleed.

Treatment is divided into prophylactic treatment to prevent bleeding episodes and emergency treatment as indicated in the acute phase of clinically significant major bleedings. Prophylactic treatment is recommended for patients with severe disease, defined as FVII:C below 1% with recurrent bleeding episodes.\(^{[9]}\) Several treatment options are available. Fresh frozen-plasma (FFP) is widely available and specially suitable for resource-limited settings. But factor VII concentrations are low in FFP. Plasma-derived FAVIId (pDFVII) and Recombinant (rFVII) are equally effective for acute bleeding and prophylactic purpose.\(^{[10]}\) The most limiting factor in use of our setting is the prohibitive cost.

Unfortunately our patient is unable to afford prophylaxis with rFVIIa. So he has been put of FFP prophylaxis thrice weekly. The bleeding episodes continue to occur intermittently though.

Message for Primary Care Physicians

An otherwise well child with complaints of spontaneous onset multi focal bleedings with isolated prolonged PT should raise the suspicion of a congenital FVII deficiency. Low factor VII values of less than 1% usually have severe phenotype with early onset, frequent and severe bleedings. Mutation studies may help in predicting phenotype. We need to systematically work up a case of bleeding child to establish diagnosis of this relatively rare but potentially treatable condition.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mariani G, Bernardi F. Factor VII deficiency. Semin Thromb Hemost 2009;35:400-6.
2. Tripathi P, Mishra P, Ranjan R, Tyagi S, Seth T, Saxena R. Factor VII deficiency – an enigma; clinicohematological profile in 12 cases. Hematology 2019;24:97-106.
3. Mariani G, Herrmann FH, Dolce A, Batorova A, Etro D, Peyvandi F. Clinical phenotypes and factor VII genotype in congenital factor VII deficiency.
4. Napolitano M, Giansily-Blaizot M, Dolce A, Schved JF, Auerswald G, Ingerslev J, et al. Prophylaxis in congenital factor VII deficiency: Indications, efficacy and safety. Results from the seven treatment evaluation registry (STER). Haematologica 2013;98:538-44.

5. Jaffray J, Young G, Ko RH. The bleeding newborn: A review of presentation, diagnosis, and management. Semin Fetal Neonatal Med 2016;21:44-9.

6. Khair K, Liesner R. Bruising and bleeding in infants and children – a practical approach. Br J Haematol 2006;133:221-31.

7. 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.

8. Herrmann FH, Wulff K, Auerswald G, Schulman S, Astersmark J, Batorova A, et al. Factor VII deficiency: Clinical manifestation of 717 subjects from Europe and Latin America with mutations in the factor 7 gene. Haemophilia 2009;15:267-80.

9. Olson NC, Raffield LM, Lange LA, Lange EM, Longstreth WT, Jr, Chauhan G, et al. Associations of activated coagulation factor VII and factor VIIa-antithrombin levels with genome-wide polymorphisms and cardiovascular disease risk. J Thromb Haemost 2018;16:19-30.