



CASE REPORT

Recurrent Venous Thromboembolic Events in a Child with Severe Factor X Deficiency

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ABSTRACT

Congenital factor X deficiency is a rare autosomal recessive bleeding disorder that presents with variable bleeding tendency and prolonged coagulation tests, prothrombin time, and partial thromboplastin time. Thromboembolic events have not been reported in patients with factor X deficiency yet. Herein, we report a patient with factor X deficiency who had recurrent venous thromboembolic events.

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Introduction

Factor X deficiency is a rare autosomal recessive severe bleeding disorder with a worldwide incidence of 1:500,000-1,000,000.¹ According to last report of the World Federation of Hemophilia's annual global survey 2014, 1655 cases of factor X deficiency has reported to date.² A wide spectrum of clinical symptoms ranging from minor bleeding, excessive bleeding after trauma or surgery and rarely hemarthrosis to life threatening bleeding has been described in the affected person.³ The diagnosis of factor X deficiency is based on coagulation tests prothrombin time (PT), activated partial thromboplastin time (aPTT), Dilute Russell's viper venom time and chromogenic assay to measure the coagulant activity of factor X (FX:C) and then if possible by immunoassay to detect plasma Factor X antigen levels (FX:Ag).² No thromboembolic event has ever been reported in patients without any history of previous treatment with coagulant products. Here we report a patient with severe factor X deficiency presenting

with recurrent venous thromboembolic events.

Case Report

An 8-year-old boy who was a known case of severe factor X deficiency was referred to Mofid Children's Hospital with abdominal pain. The diagnosis of factor X deficiency was made at 3 years of age based on bruising in the extremities which was confirmed by coagulation test assays and factor X level of 0.3% was documented in the patient. Further molecular studies at the age of 6 showed a homozygous p.Gly363Ser mutation at the encoding gene for factor X which is located on chromosome 13 (13q34). He was admitted with impression of appendicitis or intra-abdominal bleeding for evaluation of abdominal pain. Physical examination was unremarkable for guarding or rebound tenderness. Radiological findings were not conclusive. After a couple of hours the patient's abdominal pain subsided and he complained of a localized severe inguinal pain. Doppler ultrasound study showed

a decrease in the venous blood flow of common femoral vein along with a large thrombosis extending from it to the right saphenous vein. During the past two months he had not received any plasma or prothrombin complex concentrate products. A comprehensive laboratory assessment did not show any significant finding except for a protein S activity of 32% which was not clinically significant. The patient was scheduled to receive simultaneously FFP and low molecular weight heparin (LMWH). After clinical and radiological improvement, the patient continued the treatment for about 45 days. Two weeks after the cessation of FFP and LMWH the patient referred to our clinic with a severe pain in left upper extremity which Doppler ultrasound again showed a thrombosis in the left brachial vein. The patient was treated again with FFP and LMWH for one month until clinical and radiological findings were improved.

Two years later he also developed a deep venous thrombosis in the left femoral vein which was treated as before. Continuous therapy with FFP and LMWH or vitamin K antagonists was not considered for the patient due to the risk of bleeding regarding the underlying disease and lack of monitoring facilities. Currently, the patient is not receiving any product or anticoagulation treatments and is being observed for on-demand therapy.

Discussion

Factor X deficiency is a rare bleeding disorder inherited as autosomal recessive which was first described in two patients independently. The factor is also known as Stuart-Prower factor. It is a Vitamin K dependent glycoprotein which is changed to its active form as a serine protease both by factor VII and calcium, with tissue thromboplastin in the extrinsic pathway. Factor Xa is also involved in the macromolecular complex formation with its cofactor Va, tissue phospholipid and calcium to convert prothrombin to thrombin.³ Acquired deficiencies of factor X is reported most commonly with plasma cell dyscrasia and primary amyloidosis; however, there are few reports of acquired deficiency with anticoagulant treatment, liver dysfunction, treatment with phenytoin and viral infections.⁴ The factor X production is encoded by a gene of 27 kb located on chromosome 13.³ Patients with severe FX defects tend to be the most seriously affected comparing with other rare bleeding disorders.² Although the more severely affected patients (FX activity <1%) present early in life with umbilical or central nervous system (CNS) bleeding, the bleeding tendency may appear at any age. Patients with severe deficiencies commonly experience hemarthrosis and hematomas.^{3,5} However, gastrointestinal, umbilical cord bleeding, hematuria and CNS bleedings may also occur.^{5,6}

There are some reports of thrombotic events in other bleeding disorders such as hemophilia A and B, VWD, factor VII deficiency, hypofibrinogenemia and dysfibrinogenemia, although thrombotic events in factor X and FII deficiency except in the setting of over-dosage of plasma products have not ever been reported. Girolam and colleagues explained the clinical significance of the lack of arterial or venous thrombosis in patients with

congenital prothrombin or FX deficiency and they have concluded that lack of any thrombotic events in these two conditions is the rationale for use of direct thrombin or factor X inhibitors in the prophylaxis and/or therapy of thrombotic manifestations.⁷ We did not find any explanation for recurrent venous thromboembolic events in our case despite performing extensive assays. Our patient had a mild decrease in Protein S activity which might be due to heterozygosity for protein S deficiency. Although, sustained deep venous thrombosis, superficial thrombophlebitis or pulmonary embolism were reported in 74, 72, and 38 percent of 71 protein S deficient persons from 12 Deutch pedigrees, the mean age of the first thrombotic event was 28 years with a range between 15 and 68 years; 56 percent of the episodes were apparently spontaneous and the remainder were precipitated by an identifiable factor.⁸ Our patient was also heterozygote for MTHFR A1298C mutation, but the homocysteine levels in two occasions were normal. However, false negative and normal homocysteine level has been reported in MTHFR mutation.⁹ It may be related to high folate diets or increased activity of bypassing enzyme pathways. Since there was no other underlying disorder in our patient, co-inheritance of heterozygote Protein S deficiency and mutated MTHFR A1298C may be the sole explanation for thrombotic events in our patient.

The most problematic issue in this case was the management of thrombotic events since LMWH was not expected to be efficient in severe factor X deficient patient and warfarin could not be monitored by PT in this case of severe deficiency of a common pathway factor. We used a combination of antithrombotic along with FFP simultaneously until the clinical response ensued.

Conclusion

Thrombotic events is reported rarely in a variety of bleeding disorders, but in severe deficiency of factor X has not been reported yet. Its occurrence need to be evaluated for possible co-inheritance of thrombophilic disorders. There is also a challenge in management of these thrombotic events in terms of treatment and its monitoring.

Conflict of Interest: None declared.

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