

Isolated factor V deficiency in a patient with elevated PT and aPTT during routine pre-operative laboratory screening

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Abstract: Isolated factor V (FV) deficiency is a rare disorder with approximately 150 cases reported in the literature since 1943. Bleeding symptoms from FV deficiency vary widely. FV deficiency usually manifests early in the life. We present a 59-year-old case with FV deficiency discovered during pre-operative laboratory screen.

Keywords: Factor V deficiency (FV deficiency); coagulopathy; hemostasis

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Introduction

FV deficiency, also known as Owren's disease, parahemophilia, was first described in 1943 by Dr. Paul Owren in a patient having severe bleeding tendency due to the deficiency of a previously unknown coagulation factor (1,2). It is an autosomal recessive disorder with an incidence of about 1 in 1 million (3-5). The most common genetic defect is mutation of the F5 gene on the long arm of chromosome 1q23 (5). FV belongs to the family of multicopper oxidases, and is homologous to coagulation factor VIII. The gene covers 70 kb with 25 exons and encodes a large protein of 330 kDa. Heterozygous patients are usually asymptomatic. Missense, nonsense, frameshift, and splice mutations in F5 gene have been described (6).

FV is activated to FVa by thrombin and factor Xa (FXa), which eventually cleaves prothrombin to thrombin (7). FV is an essential cofactor of the complex and increases prothrombin activation by several times (8,9).

FV is a clotting factor synthesized by the liver and acts in the common pathway of the coagulation cascade. About 80% of FV circulates in the plasma whereas the remaining 20% is platelet bound (1). Symptoms of FV deficiency vary widely. FV deficiency usually manifests early in the life. We present a case of FV deficiency who presented rather later in the life.

Written informed consent was obtained from the patient for publication of this case report.

Case presentation

A 59-year-old gentleman from Pakistan with no significant past medical history presented with sudden onset of severe scrotal pain and enlargement. The patient presented to local emergency room. Patient was diagnosed with a non-obstructed left inguinal hernia and was scheduled for elective surgical repair. Patient was incidentally found to have an abnormal coagulation profile on the pre-operative blood work and patient was transferred to tertiary care center for further management. Patient's blood work showed prothrombin time (PT) of 31.5 s (normal range, 10-13 s) and activated partial thromboplastin time (aPTT) of 59.0 s (normal range, 23-36 s). Repeat blood work two days later showed PT of 32.3 s, aPTT 77.4 s and international normalized ratio (INR) 3.2. He denied taking any prescription, non-prescription or herbal medications. He was not aware of any abnormal coagulation profile in the past. Patient, however, has not had medical evaluations in the past decade. He reported history of motor vehicle accident 20 years before presentation for which he had a prolonged hospitalization (~6-8 weeks) and tooth extraction

~3 years before presentation. However, he could not recollect any evidence of excessive bleeding in either of the episodes. There was no family history of bleeding tendency.

Mixing studies with normal plasma showed that PT corrected from 36 to 11.0 s and aPTT from 67.9 to 27.2 s. This is consistent with factor deficiency. Individual factor assays were done which showed severely reduced FV levels of 0.5% (normal range, 50-150%). Factor VIII was elevated to 226% and von Willebrand factor was raised to 220%. Factor II and factor X levels were 96% and 102% respectively. Fibrinogen (factor I) was 458 mg/dL (normal range, 180-400 mg/dL). Liver function tests (LFTs) were normal [AST: 41 U/L (normal range, 4-35 U/L), ALT: 41 U/L (normal range, 6-55 U/L), Alkaline Phosphatase: 133 U/L (normal range, 40-150 U/L), total Bilirubin: 0.8 mg/dL (normal range, 0.2-1.3 mg/dL)]. Hematocrit and Platelets were normal. Normal LFTs, platelets and hematocrit ruled out any microangiopathy including DIC.

Patient received four units of fresh frozen plasma (FFP) as loading dose (15-20 mL/kg) which improved FV levels to 13% and INR corrected from 3.36 to 1.63. Patient received an additional four units of FFP prior to surgery with improvement of FV levels to 26%. Patient successfully underwent open abdominal hernia repair without any bleeding complications. Patient was closely monitored for bleeding for five days post surgery with daily clinical assessment and once daily coagulation profile (PT, aPTT, INR). Patient was transfused one unit of FFP for any INR >1.5. FV level was 23% on the first post-operative day. The patient received two additional units of FFP. Patient was discharged on day 6 post surgery without any complications.

Discussion

This asymptomatic case of isolated FV deficiency was discovered due to abnormal PT and aPTT during pre-operative laboratory screening. It is unclear whether this patient has homozygous mutation of the F5 gene, since the mutation analysis was not performed. The patient has no children, and no apparent family history was reported.

Isolated FV deficiency is a rare disorder with approximately 150 cases reported in the literature since 1943 (10). Symptoms are usually mild and mostly associated with easy bleeding or bruising. According to the "American Rare Bleeding Disorder Registry", among 18 subjects with homozygous FV deficiency (median activity <0.01 U/mL),

18% had positive family history, 76% has prior bleeding history and only 6% had abnormal values in pre-operative laboratory screen. Eventually all the subjects developed some bleeding. Forty-four percent had skin and mucosal bleeding, 23% had bleeding in joints and muscles; genitourinary and gastrointestinal bleeding was seen in 19% and 6% patients, respectively. Among 19 subjects with heterozygous FV deficiency (median activity 0.35 U/mL), 44% had positive family history, 17% has prior history of bleeding and 39% had abnormal preoperative laboratory screen. Out of the 50% patients in the heterozygous group who developed bleeding, 62% had skin and mucous membrane bleeding, while gastrointestinal and genitourinary bleeds were seen in 19% each (11). Despite the low levels of FV, our patient apparently never had prior history of easy or excessive bleeding. These different phenotype pictures have been attributed to varying activity of platelet FV activity. A European study reported four patients with congenital severe FV deficiency, yet residual platelet FV activity with low tissue factor pathway inhibitor level support appropriate thrombin generation in patients with severe FV deficiency (11).

FV deficiency is typically suspected in a patient with symptoms of bleeding in childhood and has an elevated prothrombin and partial thromboplastin time, which should be corrected after mixing study with normal plasma. Low FV levels should be evaluated for congenital deficiency, liver disease, inhibitors and antibodies. One must also measure FVIII levels to rule out combined FV and FVIII deficiency (12). FV and FVIII share about 40% sequence identity. In cases where mixing study fails to correct abnormal PT and PTT, history of exposure to bovine thrombin during prior surgical procedures may be an important clue to diagnose acquired FV inhibitor. Inhibitor presence is typically confirmed using a Bethesda assay.

Since there are neither FV concentrates nor recombinant FV available at this time, FFP remains the mainstay of treatment. Patients are generally treated after bleeding episodes or in preparation for surgery, as was the case with our patient (13). For patients with FV inhibitors, steroids, plasmapheresis, immunoabsorption, intravenous immunoglobulin, cyclophosphamide, rituximab have been tried (10,14-17).

Conclusions

FV deficiency is a rare bleeding disorder but must be considered in all patients with concomitantly elevated

prothrombin and partial thromboplastin times. The disorder, though common in early life, can manifest in the elderly as well, as a result of undiagnosed congenital deficiency or acquired deficiency due to antibodies or liver disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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