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A RARE COAGULATION DISORDER - FACTOR X DEFICIENCY

PRASANNA KARTHIK SUDHAKARAN
Department of General Medicine,
MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract :
29 year old female presenting with hematuria and recurrent episodes of bleeding manifestations since childhood was evaluated. She had no other specific complaints. She had an affected younger sibling also. Her aPTT was prolonged with normal platelet counts, Bleeding time, Prothrombin time and Thrombin time. Evaluation using mixing studies revealed the presence of Factor X deficiency. Her parents were also asymptomatic carriers of the disease. Factor X is the zymogen of factor Xa, a Vitamin K dependent serine protease. It is the first enzyme in the common pathway of thrombus formation. Factor X is otherwise called the Stuart-Prower factor. It is one of the world's most rare factor deficiencies with an estimated frequency of 1 in one million persons. Phenotypically, factor X deficiency is classified as either type I, distinguished by reduced factor X activity and reduced factor X antigen, or type II, distinguished by reduced factor X activity but normal factor X antigen. CRM -negative is type I and CRM-reduced to CRM-positive is type II. Factor X deficiency is associated with normal thrombin times but prolonged PT and aPTT, particularly among the CRM-negative variants. Unfortunately, factor X deficiency variants have been described with isolated prolonged PT or aPTT values. Treatment is infusion of fresh frozen plasma or Purified Prothrombin Complexes
Keyword : Factor X deficiency, coagulation disorder, prolonged aPTT

Case Summary:
A 29 year old female presented to the OPD with complaints of four episodes of small quantity blood stained urine since the previous day. She had no episodes of fever, abdominal pain, pedal edema, facial puffiness, decreased urine output or other bleeding manifestations. She gave history of previous episodes of similar bleeding starting at the age of 8 months and prolonged bleeding episodes following trivial injuries. She had been treated for hemarthrosis of the knee at age of 8 years and was advised further evaluation but her parents declined it. She had been transfused multiple units of plasma for her bleeding manifestations. She attained menarche at 13 years of age and had 4/28 days cycles associated with menorrhagia for which she was started on antifibrinolytics and iron supplements.

She was the fourth born of five siblings of a second degree consanguineous marriage. Her parents and elder siblings, two brothers and sister were healthy with no complaints. Her younger sister, aged 21 years had similar complaints starting from infancy. Her examination revealed significant pallor and other systemic examination was unremarkable. The provisional diagnosis was made of an inherited coagulation disorder and the patient was convinced about detailed evaluation. Haematologist opinion was sought for further evaluation. Her complete blood count showed anemia (Hb 7.6g/dL) with normal platelet counts (1.76 lakhs/ cu.mm). Her bleeding time was 2min 30sec. Her Prothrombin time was 17.5 sec and INR was 1.39. Her aPTT was 82.0 sec (N: 23.8-37.4 sec). She was transfused three units of packed RBC's and eight units of fresh frozen plasma in total to control her bleeding. She was advised to undergo further evaluation using mixing studies.The reports for her aPTT correction studies were ½ Patient + ½ control plasma: 39.5 sec, ½ Patient + ½ aged serum: 27.1 sec, ½ Patient + ½ Adsorbed plasma: 80.5 sec, ½ Patient + ½ factor X deficient plasma: 77.5" sec. Her Thrombin Time was 12.5 sec. This established her diagnosis of Factor X deficiency. Since she had a symptomatic sister with asymptomatic parents, the suspicion of carrier state of the parents was entertained and they were also evaluated. The mother's reports were PT: 12.7 sec, INR: 1.05, aPTT: 37.9 sec, aPTT correction studies with ½ Patient + ½ control plasma: 33.6 sec, Factor X assay (PT based): 87.7%, Factor X assay (aPTT based): 29.5%. The father's reports were PT: 12.6 sec, INR: 1.04, aPTT: 39.1 sec, aPTT correction studies with ½ Patient + ½ Control plasma: 33.4 sec, Factor X assay (PT based): 88.8%, Factor X assay (aPTT based): 35.4%. The patient serum was not assayed for factor X levels as she had been recently transfused.

DISCUSSION Factor X is the zymogen of factor Xa, a Vitamin K dependent serine protease. It is the first enzyme in the common pathway of thrombus formation. It is activated either by the contact-activated (intrinsic) pathway or by the tissue factor (extrinsic) pathway. Factor Xa, in combination with factor V, then activates prothrombin to form thrombin which then converts fibrinogen into fibrin. Factor X is otherwise called the Stuart-Prower factor after Mr Stuart and Miss Prower were the first persons shown to have this abnormality. It is one of the world's most rare factor deficiencies with an estimated frequency of 1 in one million persons[1]. Factor X deficiency can be inherited or acquired, with autosomal recessive inheritance being more common and with heterozygotes most often remaining asymptomatic. This condition is more among communities were the prevalence of consanguineous marriages are predominant. The most frequent symptom is epistaxis with menorrhagia occurs in half of the women of reproductive age. Soft tissue bleeding occurs in two-thirds of the patients. Spontaneous hemarthoses led to severe arthropathy. The bleeding tendency of factor X deficiency is severe and correlates with factor levels. Pedigree analysis of patients with congenital factor X deficiency often reveals consanguinity. The human gene encoding factor X is primarily expressed in the liver and is located on the long arm of chromosome 13, just downstream from the gene for factor VII. The gene for factor X shows significant homology with those coding for other vitamin K dependent serine proteases, which suggests all of these multidomain genes evolved from a common ancestral gene. It is synthesised in hepatocytes as a single

488 amino acid chain from the coding gene and later undergoes proteolytic processing in the ER to form a two chain structure which is the zymogen form. Vitamin K is required for the gamma carboxylation of the first 11 glutamic acid residues in the amino-terminal portion of the human molecule which are responsible for the calcium and phospholipid binding during the process of its activation of prothrombin. Phenotypically, factor X deficiency is classified as either type I, distinguished by reduced factor X activity and reduced factor X antigen, or type II, distinguished by reduced factor X activity but normal factor X antigen. CRM-negative is type I and CRM-reduced to CRM-positive is type II. A positive test for CRM implies that a substance that is antigenically similar to the normal coagulation factor is present in the plasma. A coagulation dpisorder characterized by the presence of such a substance often is described as a CRM-positive or qualitative disorder or variant. A negative test for CRM indicates the absence of antigenically competent protein and suggests that the disorder is caused by deficient biosynthesis of the requisite factor. The CRM-negative form is a product of missense, insertion, or deletion mutations, and is characterized by a true deficiency of factor X, with a strong correlation between functional assays and immunoassays. The CRM-reduced and -positive forms are products of missense mutations and are characterized by low to normal levels of antigenically competent factor X but with disproportionately reduced factor X activity.[2] Factor X deficiency is associated with normal thrombin times but prolonged PT, aPTT, and often Stypven (Russell viper venom) time, particularly among the CRM-negative variants. Unfortunately, factor X–deficiency variants have been described with isolated prolonged PT or aPTT values.[3,4] The heterozygotes generally appear asymptomatic, as hemostasis can be maintained by factor X levels >10% of normal. On the other hand, compound heterozygotes and homozygotes with factor X levels <1% of normal suffer from severe bleeding. Treatment is infusion of fresh frozen plasma at a dose of 15–20 ml/kg and for treatment and 5–10 ml/kg daily as maintenance or Purified Prothrombin Complexes at a dose of 15 IU/kg for treatment and 10 IU/kg daily for maintenance. Immunogenetic studies should be carried out in these patients to delineate which of the mutations are prevalent among South Indian populations.

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