

Factor XII Deficiency: Two Cases about A Rare Coagulation Disorder in a Pediatric Hematology-Oncology Department

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Abstract

Factor XII (FXII) deficiency is a rare autosomal recessive inherited disorder that causes a significant prolongation of activated partial thromboplastin time (aPTT), imitating a coagulation disorder. The distinctive feature of FXII deficit is the absence of clinical bleeding complications and the tendency to thromboembolic events. Our work concerns two patients with factor XII deficiency. At the time of diagnosis, the patients were aged between 10 months and 2 years with no significant medical history. Neither patient presented with hemorrhagic syndrome, with an extended APTT being discovered incidentally during pre-operative testing.

Keywords: factor XII deficiency; inherited disease; coagulation; thromboembolic events

Introduction

Factor XII deficiency is a rare autosomal recessive disease, with few reported cases of dominant transmission, whose the incidence is less than 1/1,000,000 [1]. Rarely, the deficiency is acquired, following nephrotic syndrome, sepsis or disseminated intravascular coagulation [2]. FXII, known as Hageman Factor, is a glycoprotein synthesised by the liver and encoded by the F12 gene located on the long arm of chromosome 5 [3]. FXII is a key protein in the intrinsic pathway of coagulation, by activation of plasmin into plasminogen, measured by activated partial thromboplastin time (aPPT) [4]. Factor XII deficiency is often incidentally discovered. Unlike the other coagulation factors, factor XII deficiency preserves the physiological activity of hemostasis in vivo resulting in the absence of hemorrhagic syndrome [1].

Case 1

A 11-month-old infant from a consanguineous marriage, third of four siblings, with a paternal cousin being treated for factor XII deficiency. The history of the disease dates back to one month before his consultation, when the patient was a candidate for circumcision. The patient carried out a preoperative testing, which revealed abnormalities in hemostasis. The clinical examination shows a child without fever, hemodynamically stable, with no cutaneous or external hemorrhagic syndrome.

The abdominal examination shows a dispersible abdomen with no hepatomegaly or collateral venous circulation.

Laboratory testing revealed a hemoglobin of 11 g/dL (normal range 9.5 - 13.5 g/dL) and hematocrit of 38% (normal range 30% - 42%), prolonged aPTT at 120 seconds (normal range 25-35 seconds). Prothrombin time (PT) was at 100% (normal range 70-100%). Aspartate aminotransferase (AST) at 56 U/L (normal <35 U/L), alanine aminotransferase (ALT) at 64 U/L (normal range <40 U/L), alkaline phosphatase was normal at 35 U/L (normal range 35-130 U/L) and gamma-glutamyl transpeptidase (GGTP) at 25 U/L (normal range <60 U/L). The abdominal ultrasound shows a spleen and liver of normal size with no effusion or other detectable abnormalities. Viral serology tests are negative (including hepatitis A, B and C). The Disseminated intravascular coagulation test results are normal, with normal fibrinogen (normal range 185-408 mg/dL) and normal D-dimer levels (normal range <0.53 mg/L FEU). Given this biological profile, coagulation factor testing was performed, showing factor VIII at 78% (normal range 55-180%), factor IX at 68% (normal range 65-140%) and factor XII at 2% (normal range 65-130%).

The infant is diagnosed with factor XII deficiency without any clinical symptoms. Biological monitoring is recommended, and the surgery is not performed.

Case 2

A 3-year-old child born to consanguineous parents, second of three siblings. He presented a physiological jaundice in the neonatal period. The child had never presented with hemorrhagic syndrome until the age of 2, when the patient was scheduled for circumcision and preoperative testing revealed hemostasis abnormalities.

The clinical examination shows a child without fever, hemodynamically stable, with no cutaneous or external hemorrhagic syndrome. The abdominal examination shows a dispersible abdomen with no hepatomegaly or collateral venous circulation.

Laboratory testing revealed a hemoglobin of 9.6 g/dL (normal range 9.5 - 13.5 g/dL) and hematocrit of 36% (normal range 30% - 42%), prolonged aPTT at 130 seconds (normal range 25-35 seconds). Prothrombin time (PT) was at 100% (normal range 70-100%). Aspartate aminotransferase (AST) at 50 U/L (normal <35 U/L), alanine aminotransferase (ALT) at 54 U/L (normal range <40 U/L), alkaline phosphatase was normal at 46 U/L (normal range 35-130 U/L) and gamma-glutamyl transpeptidase (GGTP) at 37 U/L (normal range <60 U/L). The Disseminated intravascular coagulation test results are normal, with normal fibrinogen (normal range 185-408 mg/dL) and normal D-dimer levels (normal range <0.53 mg/L FEU). The abdominal ultrasound shows a spleen and liver of normal size with no effusion or other detectable abnormalities. Viral serology tests are negative (including hepatitis A, B and C). Given this biological profile, coagulation factor testing was performed, showing factor VIII at 199% (normal range 55-180%), factor IX at 104% (normal range 65-140%), factor XI at 98% (normal range 70-140%) and factor XII at 3% (normal range 65-130%).

The infant is diagnosed with factor XII deficiency without any clinical symptoms. Biological monitoring is recommended, and the surgery is not performed.

Discussion

Factor XII, or Hageman factor, is a glycoprotein responsible for initiating the intrinsic pathway of the clotting cascade [5]. The FXII gene measures 12 kb, has 14 exons and 13 introns. It is located on chromosome 5q35.3 [6]. Mutation of the F12 gene, either homozygous or compound heterozygous, results in factor XII deficiency [2]. Most often, it is an autosomal recessive mutation discovered incidentally by the appearance of a biological abnormality: an isolated prolonged activated partial thromboplastin time (aPTT) [7]. The prolonged aPTT may be observed in patients receiving anticoagulant treatment or with liver disease. Otherwise, prolonged aPTT should be investigated to detect any underlying pathology or abnormality, as it may suggest the presence of antiphospholipid antibodies or anti-factor VIII antibodies [1]. After these etiologies are excluded, a correction study is performed. Afterwards, aPTT and PT are performed immediately and after incubation at 37°C. Correction at both determinations indicates coagulation factor deficiency of one or more coagulation factors. Dosage test of factors VIII, IX, XI and XII are carried out [8]. Bleeding disorders related to deficiencies of factors VIII, and IX result in the hemophilia A and hemophilia B respectively [9]. Alternatively, FXII deficiency does not cause a bleeding

disorder [3].

Factor XII is the zymogen of the protease enzyme called activated factor XII (FXIIa) which binds to negatively charged surfaces (contact activation) [10]. Factor XIIa converts prekallikrein to kallikrein, successively the kallikrein cleaves FXII to heavy chain alpha-FXIIa and light chain beta-FXIIa [11]. Alpha-factor XII converts plasminogen into plasmin playing an important role in fibrinolysis. Furthermore, factor XII increase the production of bradykinin, a protein that stimulates inflammation by improving the permeability of the vascular wall [7]. FXII is also activated by an inorganic phosphate polymer (Poly P) that exists on platelet dense granules. This demonstrate a role for poly P-mediated FXII activation among inflammation and thrombosis [12]. Recently, animal model research studies on FXII deficiency has demonstrated normal hemostasis in the presence of defective thrombus formation, with protection from pulmonary embolism and cerebral ischemia [4].

In this study, A genetic study was not conducted to determine whether the deficiency was homozygous or heterozygous. Given the unpredictable nature and the rarity of the disease, both patients were monitored regularly. Family screening was not performed because the patients did not develop any symptoms afterwards. However, family screening is recommended in future studies, given the rarity of FXII deficiency and the importance of the findings in such cases.

Conclusion

This study presents two patients with incidental discovery of factor XII deficiency on prolonged partial thromboplastin time during preoperative testing. Treatment of these patients is difficult due to the rarity of such cases and the unavailability of factor XII replacement therapy in our setting. It is recommended that data on these cases be shared in order to enrich the data available from clinical practice.

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