Doi: 10.32677/IJCH.2016.v03.i04.020

Case Report

Factor XII deficiency - A rare coagulation disorder

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Received – 02 July 2016 Initial Review – 30 July 2016 Published Online – 12 Sept 2016

ABSTRACT

Severe coagulation factor XII (FXII) deficiency is a very rare, mysterious, and not well-known inherited condition. Unlike other coagulation factor deficiencies, it is usually asymptomatic in most of the cases. Congenital FXII deficiency is the most common cause of an isolated prolongation of the activated partial thromboplastin time in a non-bleeding child or adult; consequently, most patients are detected during a routine pre-operative coagulation study. Surprisingly, it does not lead to abnormal bleeding, but some cases of severe FXII deficiency experiences thrombotic events in their lifetime. There are only a few reports of FXII deficiency in literature. We are reporting a case of congenital FXII deficiency in a 7-month-old child.

Key words: *Factor XII deficiency, Prolonged activated partial thromboplastin time, Recurrent pregnancy loses*

Factor XII (FXII) deficiency, which is also known as Hageman factor deficiency, was first described in the medical literature by Dr. Oscar Ratnoff and Dr. Jane Colopy, in 1955, in a patient named John Hageman. The precise incidence of the disorder in the common population is still unknown, but it is found approximately 1 in 1 million individuals [1]. It is more common in Asians than other ethnic groups. FXII deficiency is inherited in an autosomal recessive fashion [2], but autosomal dominant inheritance was also reported [3]. Soria et al. [4] conducted a genome-wide linkage screen to confine genes that influenced the variation in levels of FXII. Two genetic loci were detected on chromosome 5 and 10. Hereditary coagulation FXII deficiency is also identified in a patient with heterozygous missense mutation at exon 13 of FXII gene [5].

FXII is a beta-globulin serine protease (single chained) with a molecular weight of 80,000-84,000 Da and a plasma concentration of 30 pg/mL, respectively. Proteolytic cleavage of FXII is mediated by charged surfaces (kaolin, glass, dextran sulfate, cellulite, endotoxin, crude collagen, urates, and sulfatides), kallikrein, and autoactivation. Prekallikrein, FVII, FXI, complement C1, and plasminogen are cleaved by activated FXII proteolytically (FXIIa) into their active forms [6]. FXIIa plays a dual role in the cascade reactions of coagulation. It can stimulate FXI, which, in turn, activates FIX (previous intrinsic pathway); however, this is its marginal function. The major function is the conversion of plasminogen into plasmin which takes place with the help of activated FXII and initiation of fibrinolysis. In the human body, processes of fibrinolysis and coagulation are constantly in a dynamic equilibrium; therefore, factor deficiency can potentially increase the risk of thrombosis [7].

In a non-bleeding child or adult, congenital FXII deficiency is the familiar cause of an isolated prolongation of activated partial thromboplastin time (aPTT). Most patients are detected during a routine pre-operative coagulation study [8]. Most of the patients resist severe challenges to the hemostatic system, such as major surgery or dental extractions without bleeding; although, epistaxis or easy bruising has been reported in FXII deficient patient occasionally. In contrast to the usual lack of bleeding manifestations, there is an increased incidence of serious thromboembolic problems in patients with hereditary FXII deficiency. The first patient discovered to have FXII deficiency, John Hageman, died of a pulmonary embolus [9].

CASE REPORT

A 7-month-old 2nd born male child was born to a non-consanguineously married Indian couple at term by normal vaginal delivery with birth weight of 2.6 kg. At the age of 4 months, he developed multiple ecchymotic patches all over the body. These ecchymotic patches were self-resolving in nature and reappeared in every 10-15 days. History of prolong bleeding after minor trauma was present. There was no history of any bleeding disorder in any other family member. The child was exclusively breastfed till the age of 3 months, and thereafter, weaning started with buffalo milk and biscuits.

On physical examination, multiple ecchymotic patches were present over the trunk, back, arms, and legs, largest measuring 3 cm × 2.5 cm (Fig. 1a and b). Except undernutrition: Weight 6.8 kg (−2SD to −3SD), growth, and development were within normal limits (occipitofrontal circumference 44 cm [between −1SD and +1SD], length 65.5 cm [between −2SD and −1SD]). Systemic examination was normal.

On blood investigation, complete blood count revealed microcytic hypochromic anemia (hemoglobin 9.7 g/dL). Platelet count was 547,000/mm^3. Renal and liver function tests were within normal limits. During the hospital stay, the patient was given vitamin K and supportive treatment. Documented evidence of persistent elevation of aPTT at our center is listed in Table 1. To find out the cause of excessively raised level of aPTT, investigation to measure the concentration of clotting factor was

sent which revealed following parameters as listed in Table 2.

We found the low level of FXII in this case, which is a rare disorder; so we are reporting this case. Since the child showed no evidence of gross bleeding during his hospital stay, so vitamin K was stopped and discharged on iron-folic acid, calcium, and vitamin D drops. The patient has been advised for regular follow-up at our center (at least every 3 months). The possibility of occurrence of thromboembolic complications has been explained to the parents.

DISCUSSION

Deficiency of coagulation FXII is either acquired or congenital. Acquired FXII deficiency is found in patients who has nephrotic syndrome. The pathological basis of this deficiency has not been recognized since the urinary loss of FXII is not only the cause for the reduced plasma activity. Other causes of acquired FXII deficiency are liver transplantation, autoimmune diseases, in association with von Willebrand disease, FVIII or FIX deficiency, high molecular weight kininogen deficiency, heparin contamination, liver diseases, prekallikrein deficiency, and lupus anticoagulants [10].

Another kind of coagulation deficiency is congenital coagulation FXII deficiency which is a rare autosomal recessive hereditary disease. Its manifestations are low factor concentration without significant bleeding. As a result, deficiency of coagulation FXII is often diagnosed by regular coagulation tests conducted before surgeries. Since no severe bleeding occurs, there is not any requirement of specific treatment [11].

There have been lots of reports of association of Hageman factor deficiency of myocardial infarction (MI), and recurrent pregnancy losses. Therefore, on detection of Hageman factor deficiency, clinician must think about these associated risks in female patients rather than internal or visible bleeding. The patient of low Hageman factor can die due to acute MI and pulmonary embolism. So, better risk management is must for the better prognosis of individuals affected with FXII deficiency.

There should not be any unnecessary delay in surgical interventions and investigations that are not needed in patients of isolated FXII deficiency. In recent years, it is found that fibrinolytic effect of FXII is more important than its role in intrinsic coagulation pathway. Currently, researchers are more concerned on thrombotic complications (cardiovascular and cerebrovascular) in FXII deficiency patients [10]. As most of the patients detected with FXII deficiency are asymptomatic, so no treatment may be needed.

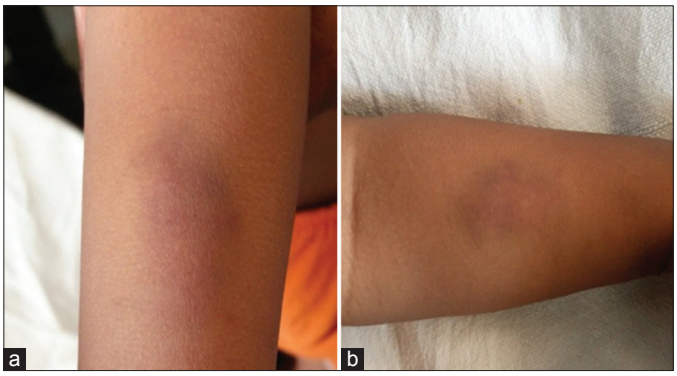

Figure 1: (a and b) Ecchymotic patches over back of arm and flexor aspect of forearm

Table 1: aPTT and clotting time during patient's stay

Date of investigation	aPTT	Clotting time
02-04-2016	89.5 s	>15 min
12-04-2016	68.5 s	>15 min

aPTT: Activated partial thromboplastin time

Table 2: Measurement of clotting factor in percentage

Clotting factor	Percentage detected	Normal limits (%)
VIII	86.0	56-191
IX	95.0	36-136
XII	40.4	70-120

CONCLUSION

FXII deficiency is associated with isolated prolonged aPTT without the risk of bleeding, so it is important to recognize deficiency of FXII in all cases of isolated prolonged aPTT to prevent unnecessary fresh frozen plasma transfusions. The delay in surgical interventions due to fear of bleeding and unnecessary investigations are not needed in patients of isolated FXII deficiency. Furthermore, these patients should be at followed up regularly due to the increased risk of thromboembolic episodes.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kumar R, Gupta A, Mathur P, Garg M. Factor XII deficiency - A rare coagulation disorder. Indian J Child Health. 2016; 3(4):349-350.