Case report

Unusual Presentation of Factor XII Deficiency with Bleeding: A Rare Case Report

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Abstract:
Factor XII (FXII) is a coagulation protein involved in the initiation of coagulation via contact activation system. Congenital FXII deficiency is a rare, asymptomatic disorder, associated with an isolated prolonged activated partial thromboplastin time (APTT). FXII deficiency is not commonly associated with any bleeding symptom except for a few cases presenting with occasional minor bleeds, which does not require treatment. Instead, a few literature reports suggest an increased incidence of various thromboembolic events in these patients. We report a rare occurrence of FXII deficiency presenting with severe bleeding symptoms.

Key words: Factor XII deficiency, contact activation system, thromboembolic events.

Introduction

Factor XII (FXII), also known as Hageman factor, is an 80 kDa plasma protein synthesized in liver. It is involved in coagulation of blood via contact activation as seen in the activated partial thromboplastin time (APTT). Activation of FXII occurs when the complex of FXII, factor XI (FXI), pre- kallikrein, and high molecular weight kininogen contact a negatively charged surface. FXII subsequently activates FXI and thus plays a role in fibrin clot formation. A rather more important role of FXII is the conversion of plasminogen to plasmin and initiation of fibrinolysis[1].

Congenital FXII deficiency is inherited as an autosomal recessive disorder with a very low incidence of approximately 1 in a million individuals.[2] Rare cases with autosomal dominant pattern have also been reported.[3] The gene for FXII is located on chromosome 5. FXII deficiency is usually asymptomatic and associated with prolongation of APTT.[4] The condition is usually diagnosed incidentally e.g. during pre-operative coagulation work up. FXII deficiency is normally asymptomatic, however, a few patients with occasional minor bleeds have been previously reported.[3] In contrast, this disorder has been associated with a significantly increased risk of thrombosis, due to impaired fibrinolytic system.[4]

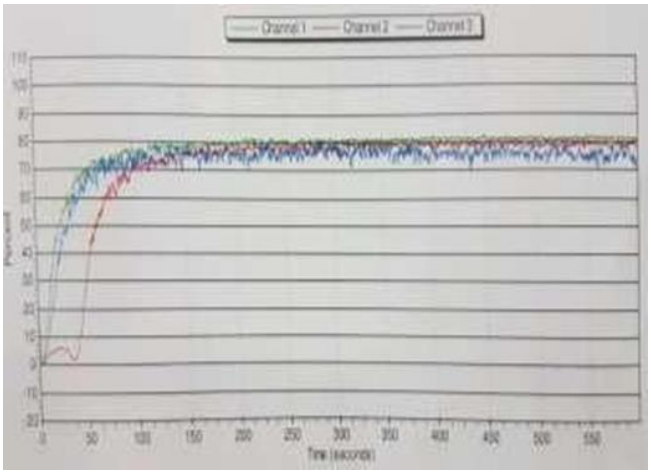
Case Report

A 17 years old female born to consanguineously married couple presented to us for diagnostic work up of a suspected bleeding disorder. She complained off and on right knee joint pain with associated swelling for the past two years. Her past history included several episodes of epistaxis, gum bleeding, per rectal bleeding, melena and spontaneous bruising since childhood. She was transfused multiple times with whole blood and plasma for the mentioned bleeding symptoms; the symptoms would resolve with the transfusions. Two years back, she underwent exploratory laparotomy and abdominal lavage due to primary peritonitis. In the process she was given multiple fresh frozen plasma (FFP) and whole blood transfusions. She also complained of menorrhagia since menarche. Her complete blood count showed haemoglobin: 12 g/dl, total leukocyte count: 5.8 x 109/l, platelet count: 196 x 109/l. Coagulation screen revealed a normal prothrombin time (PT) of 12 seconds, (reference range 10-13sec), bleeding time: 3 minutes (reference range 3-7 min) with a prolonged APTT: more than 120 sec (reference range 24-32sec). A 1:1 mixture of patient's plasma and pooled normal plasma revealed complete correction of patient's APTT, excluding the presence of any inhibitor. We further performed coagulation assays of factors VIII, IX, XI and XII, (performed on Sysmex CA 550) as these clotting factor deficiencies can cause a prolonged APTT. Our results revealed normal levels of factors VIII, IX and IX with absent FXII. Von Willebrand antigen (Sysmex CA 500) levels and ristocetin co-factor activity (Aggram Helena) were also within normal limits. As FXII deficiency is usually not associated with any bleeding symptoms we further performed fibrinogen assays (Sysmex CA 50), platelet aggregation studies (Aggram Helena) and factor XIII (FXIII) levels to rule out any concomitant pathology; all of these turned out to be normal. Work up for renal and autoimmune disorders was also done to exclude the possibility of acquired deficiency. Thus, she was diagnosed as a case of congenital FXII deficiency. Interestingly, no mutations in the factor XII gene were found on Snager's sequencing. She was put on oral hormonal contraceptive for her menorrrhagia. FFPs were given at 10ml/kg to treat right knee joint haemarthrosis after which her symptoms were resolved. She was offered physiotherapy for further management.

Discussion

FXII deficiency is a blood disorder with a very low incidence. It may be congenital, in which case it is usually diagnosed incidentally by an isolated prolonged APTT during routine coagulation screen. Other related disorders associated with a prolonged APTT include deficiency of factors VIII, IX, XI, contact factors, Von Willebrands disease as well as a few inhibitors of coagulation including lupus anticoagulant and acquired inhibitors against various coagulation factors e.g factor VIII. However, FXII deficiency is usually not associated with any bleeding manifestations, in contrast to other clotting factor deficiencies e.g factor VIII, IX etc. Another acquired form of factor XII deficiency may be caused by inhibitors against FXII. This has been reported in patients with nephrotic syndrome and leukemia.5 Conversely, these patients have an increased risk of thromboembolic phenomenon due to impaired fibrinolysis in FXII deficiency. Various researchers have reported association of FXII deficiency with myocardial infarction, pulmonary embolism and other life threatening thrombotic episodes.6

Parameter	Patient Value	Reference Range
Bleeding score	19*	-
First Line Coagulation Screening		
Bleeding time	3 min	3-7 min
PT	12 sec	10-13 sec
APTT	More than 120 sec	24-32 sec
Fibrinogen	213mg/dl	180-350 mg/dl
Intrinsic Pathway		
Factor VIII	141%	50-150%
Factor IX	91%	50-150%
Factor XI	81%	50-150%
Factor XII	0%	50-150%
Associated Factors		
Factor XIII	76%	50-150%
VWF Antigen	89%	50-200%
Ricof	94%	50-200%
Platelet disorders	Normal platelet aggregation	-
Autoimmune Work Up		
Anti ds- DNA	1.68 U/ml	<20 U/ml
ANA	<1:100 (negative)	<1:100
Renal Work Up		
Urea	20 mg/dl	10-50 mg/dl
Creatinine	1.1 mg/dl	0.7- 1.3 mg/dl
Genetic Work up		
Snager's sequencing	No mutation detected	



Platelet Aggregometry Results

Ristocetin: 80.9%

Collagen : 80.7%

ADP : 82%

Few reports have also emphasized that female patients with Hageman factor deficiency might also be at a higher risk for recurrent pregnancy losses.7, 8 Therefore, once diagnosed, these patients should be followed up closely for any thrombotic events. In a study carried out on all the available members of Swiss families affected by factor XII deficiency, it was found that patients with homozygous FXII deficiency are more likely to develop thromboembolic disease whereas partial FXII deficiency is not usually associated with thrombosis.9 However, different subsequent studies have shown that these patients developed thrombosis due to other risk factors rather than factor XII deficiency.10,11 Recently, researchers are working on newer anticoagulants targeting factor XII.11 There were a few limitations in this case report. Antigen level of FXII could not be performed because of non-availability of required resources and the diagnosis had to be made solely based on FXII activity. Similarly, we were unable to rule out any concomitant deficiency of other contact factors e.g pre-kallikrein, high molecular weight kininogen etc.

Conclusion

FXII deficiency is a rare genetic blood disorder; usually not associated with any bleeding tendencies. Moreover, these patients also do not bleed following invasive procedures such as surgery and dental extraction. Thus, these patients routinely do not need any treatment or prophylactic measures. However, as reported in our case a few patients with FXII deficiency may present with bleeding symptoms and

should be managed accordingly. A probable cause for these haemorrhagic incidents in our case might be the complete absence of FXII activity in the plasma. The purpose of this case report is to bring forth the rare occurrence of severe bleeding manifestations in patients with FXII deficiency.

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