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HAEMATOLOGY

Prolonged activated partial thromboplastin time secondary to factor XII deficiency in two surgical patients

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Abstract

Factor XII (FXII) plays a pivotal role in hemostasis, inflammation and complement system. Its deficiency is usually an incidental finding in an otherwise asymptomatic patient who is identified during his/her routine preoperative blood work. This study aimed in evaluating the clinical course of the surgical patients having FXII deficiency. Information regarding demographics, laboratory tests and management of patients was obtained through medical chart and in-house integrated laboratory management system whereas the medical literature was searched through PubMed®. During the study period, two patients were consulted for FXII deficiency prior to the various surgical procedures. Both patients had uneventful surgeries without any thrombotic events while hemorrhage observed in one patient was secondary to obstetric complications. With the limited evidence today, it is concluded that patients having FXII deficiency are not at increased risk of bleeding, thrombosis or infections during surgery, but a personalized approach is needed for planning an appropriate perioperative management.

INTRODUCTION

Factor XII (FXII) is an important physiological mediator of hemostasis, inflammation, complement system and fibrinolysis. Located on chromosome 5 with 13 exons, FXII gene encodes for a single chain of 615 amino acids requiring post translational modification for conversion to a mature 596-amino acid zymogen in the liver [1]. Exposure to negatively charged surfaces converts FXII to its active serine protease form FXIIa that triggers factor XI activation, mediates inflammation by cleaving plasma prekallikrein (PK) to its active kallikrein, activates C1r and C1s of complement system, cleaves plasminogen to plasmin during fibrinolysis [1] and activates neutrophil by interacting with uPAR receptors [2]. FXII deficiency is a rare autosomal recessive disorder with a frequency of 2.3% as reported in 300 healthy blood donors [3]. It is usually an incidental finding during preoperative blood work in an otherwise asymptomatic patient signifying dispensable role of FXII in intrinsic pathway of secondary hemostasis. Interestingly, mutations in FXII gene may lead to C1-inhibitor deficiency causing a rare disorder, hereditary angioedema without concomitant FXII deficiency. The current study described the perioperative clinical course of two surgical patients having FXII deficiency and is anticipated

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Table 1: Demographics and laboratory details of the patients having FXII deficiency at presentation

Demographics	Reference range	Proband 1	Proband 2
Age	–	26	35
Gender	–	Female	Male
Primary diagnosis	–	Pregnancy	Oligo-dendro-glioma of brain
Hemoglobin g/dl	M 13.7–16.3	–	16.4
	F 11.1–14.5	10.9	–
MCV fl	76–96	73.2	87.2
MCH pg/dl	26–32	22.0	33.0
White cell count $X10^9$/L	4–10	7.4	14
Platelet Count $X10^9$/L	150–400	333	330
Bleeding time minutes	1–7	2.5	–
PT seconds	9.1–13.1	10.3	10
APTT seconds	22.9–34.5	54.9	133.5
APTT mix 50:50 NP	–	27.3	22.1
FVIII %	50–149	89	>200
FIX %	50–163	92	140
FXI %	67–127	87	123
FXII %	52–164	3	<1
Protein C %	70–140	>150	Not done
Protein S %	56–121	48	Not done
Antithrombin III %	74–126	103	Not done
lupus anticoagulant screen (RVVT) seconds	31–44	31.7	Not done
APCR	0.86–1.10	0.99	Not done
Anticardiolipin IgG GPL/ml	<10	4.72	Not done
Anticardiolipin IgM MPL/ml	<5	0.87	Not done

to assist clinicians in investigating and managing such patients; most importantly to counsel the patient and the attending who are worried for an unexpected bleeding or thrombosis during surgery.

CASE REPORTS

First case was a 26-year-old multigravida (G_4 P_{2+1}) who presented at 18th week of gestation with a history of first trimester-fetal loss and postpartum hemorrhage in the last delivery. Her physical examination was unremarkable. Laboratory work-up is given in Table 1 that shows that she had FXII deficiency, low protein S level and a negative lupus anticoagulant screen. At 35th week of gestation, she had an emergency Caesarian-section with an estimated blood loss of 1000 ml following surgical separation of plastered uterus from anterior abdominal wall, dropping the hemoglobin to 7.7 g/dl. Four units of fresh frozen plasma was transfused during surgery while 1 gm intravenous tranexamic acid was given thrice daily for 8 days. She also received thromboprophylaxis (40 mg enoxaparin subcutaneously) for surgical procedure as per institutional protocol. Both mother and baby were discharged in a stable condition after a week. The patient showed an improvement of hemoglobin to 11.4 g/dl at three-month follow-up.

Second case was a 35-year-male who presented with seizure for few days. Computed tomography (CT) contrast showed right frontal lobe parasagittal mass. Comorbidities included Graves' disease for which he was receiving oral carbimazole. Hemostatic inquiry showed that patient had no personal or family history of bleeding or thrombosis. He was previously operated for incisional hernia and tonsillectomy; both of which were uneventful. He was planned for surgical removal of the mass. His preoperative work-up is detailed in Table 1 which shows that he had FXII deficiency. The patient underwent uneventful surgery without plasma or red cells transfusion.

DISCUSSION

The study described the clinical course of the two patients with FXII deficiency having uneventful surgical procedures.

Prothrombin time (PT) and activated partial thromboplastin time (APTT) are the routine preoperative coagulation tests. However, at least nine observational studies indicated a low positive predictive value (0.03–0.22) and likelihood ratio (0.94–5.1) for these coagulation tests for predicting surgical bleeding [4]. This may not be the case if a surgery itself is associated with a high hemorrhagic risk and where it is important to identify obscure bleeding tendency in a surgical patient having prolonged PT/APTT. A reasonable testing algorithm for prolonged PT/APTT includes the exclusion of preanalytic variables like high hematocrit, incompletely filled tube, icteric, lipemic or hemolyzed sample followed by obtaining clinical details such as a history of thrombosis, bleeding or an intake of anticoagulants and or the presence of systemic disease. The test is then repeated following an addition of normal pooled plasma (NP) in a 50:50 ratio. Although a correction of clotting time implies deficiency of clotting factors, the presence of inhibiting factors (like lupus anticoagulant or anticardiolipin antibodies) will keep the initial test result unchanged. For an isolated prolonged APTT that shows correction with NP, the final step is to perform factors VIII, IX, XI and XII assays and if possible, high molecular weight kininogen (HK) and PK.

FXII deficiency is usually found accidentally on routine coagulation screening prior to surgery in an asymptomatic patient. In a study on 8069 planned surgical patients, prolonged APTT was observed in 5.8% patients primarily due to anticoagulants usage while FXII deficiency was observed in only three of 17 patients tested for FXII assay [5]. In contrast, acquired FXII deficiency is frequent as reported by Bachler M *et al.* in 51% of his 79 critically ill intensive care patients having sepsis, renal failure and following blood transfusion [6].

The two patients with FXII deficiency in this case report underwent successful surgical procedures without any

thrombotic events during or after surgery. Patient 1 had subnormal protein S which is a usual finding in a normal pregnancy because of its increase binding to protein C4b. Her lupus anticoagulant screening was negative and therefore cannot be accounted for her single fetal loss. There was no perioperative bleeding in Patient 2 while excessive bleeding observed in Patient 1 was secondary to underlying obstetric complication and responded to the administration of tranexamic acid, an antifibrinolytic agent that is commonly used in treating obstetric hemorrhage. It is difficult to justify the transfusion decision in Patient 1; perhaps obstetrician aimed to control bleeding with normalization of APTT.

Interestingly, FXII was named after John Hageman, a 37-year-old male who was the first patient identified with FXII (Hageman factor) deficiency and died of pulmonary embolism (PE) following surgery for fractured hemipelvis [7] which might be a consequence of his postoperative immobilization unrelated to deficiency of FXII [7]. Girolami *et al*. in 2004 reviewed 24 surgical patients with inherited FXII deficiency [8] and none had any significant postoperative hemorrhage or thrombosis except for one patient who bled during nasal polypectomy. Surprisingly, 33% of the patients received whole blood and plasma therapy prior to surgery [8] without evidence for this need. Cardiac bypass surgery is a major challenge for hemostasis and is a good model for evaluating hemorrhagic or thrombotic potential in surgical patients. No bleeding or thrombotic complication was observed postoperatively in any patients having FXII deficiency who had bypass surgeries [9]. In such patients, heparin monitoring is daunting due to prolonged activated clotting time or APTT that can now be tested through heparin concentration or anti-Xa assay. FXII plays a role in neutrophil chemotaxis and activation of classical complement pathway, so individuals with low levels of FXII are theoretically at increased risk of infections with encapsulated organism. One patient with FXII deficiency so far was described having wound infection with *Escerichia coli* [10].

Though prolonged APTT secondary to FXII deficiency is well known to the hematologists but this may not be the case with surgeons, fellows and residents who deal with perioperative coagulopathy with a general tendency to transfuse plasma for correcting prolonged clotting times. These two cases highlighted the significance of hematology consultation with appropriate surgical plan for patients with FXII deficiency with personalized approach. Larger case series are required for an evidence-based approach but given the rarity of the disorder, this task is apparently difficult to achieve.

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CONFLICT OF INTEREST STATEMENT

None declared.

ETHICAL APPROVAL

Institutional ethical review committee reviewed and approved the study [No. 2019–2090-5355].

CONSENT

Informed consent was taken from individual patient prior to publication.

GUARANTOR

Bushra Moiz is the guarantor of this manuscript.

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