CASE REPORT

A Rare Case of Factor Xii Deficiency in a Pregnant Woman

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ABSTRACT

Factor XII deficiency, also known as the Hageman factor, is a rare disorder that has not been associated with any adverse outcomes. It is an interesting blood disorder whereby in the state of deficiency, it causes prolongation activated partial thromboplastin time (aPTT) which is correctable with mixing test. Although there have been case reports that have mentioned events of thrombosis and bleeding, however, no clear causal relationship has been established. Evidence for adverse events occurring in patients with Factor XII deficiency is sparse. We report here a case of a lady with a history of miscarriages who was incidentally found to have Factor XII deficiency during a routine workup for prolonged aPTT.

Keywords: Factor XII deficiency, Hageman factor, Recurrent miscarriage

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INTRODUCTION

In July 1953, a gentleman named John Hageman had been admitted to a hospital in Cleveland for a duodenal ulcer and was planned for surgery. Series of events led to the discovery of Factor XII and by extension, in 1964, the proposal of the 'waterfall' model of coagulation by Davie and Ratnoff. John Hageman would go on to make an uneventful recovery from the surgery with no bleeding events only to succumb to pulmonary thromboembolism in 1968 after sustaining a pelvic fracture (1). However, as his death occurred before the development of the advances in genetic studies, the mutations that could have contributed to this factor deficiency were not identified. Over the years, reports have emerged linking this factor XII to postpartum haemorrhages, recurrent miscarriages and thromboembolic events (2-4).

Factor XII is a circulating protease that is necessary for the initiation of the intrinsic coagulation cascade and fibrin formation. When deficient, it results in a significant prolongation of activated partial thromboplastin time (aPTT), mimicking a bleeding disorder. Recent evidence shows that this deficiency is not significantly associated with any adverse events, be it thrombotic or bleeding. However, Factor XII deficiency often draws curiosity due to its status as a rare condition.

The condition differs from recurrent miscarriages or pregnancy losses associated with antiphospholipid syndrome which is characterized by an uncorrectable aPPT level on mixing test. In cases where aPPT level can be corrected, a thorough screening for the presence of factor deficiency is mandatory.

We report here a case of a lady found to have this deficiency following a history of miscarriages and incidental discovery of prolonged aPTT on preoperative blood testing.

CASE REPORT

We report the case of a 34 years old lady with no known medical illness who presented to our obstetrics colleagues in December of 2018 with a second-trimester miscarriage at 15 weeks. On further questioning, she had suffered a previous first-trimester miscarriage in July 2017 at 6 weeks of gestation. She previously had one full term and uncomplicated pregnancy in 2011 which resulted in her current living, healthy, and only child. She had no history to suggest a connective tissue disorder or liver disease. She had no previous history of thromboembolic events. She had a negative family history for blood disorders. Physical examination revealed no obvious abnormalities either. She was planned for a dilatation and curettage procedure and preoperative blood was taken. This was when the managing team noticed that she had prolonged aPTT levels despite having three different adequate samples being sent. Her aPTT levels on 3 separate readings were 78.1 sec, 110 sec and 150 sec. Subsequently, she was referred to the haematology team for further opinion. After haematology review, it was decided that the dilatation and curettage procedure could be done. Her blood was also sent for mixing test which was corrected with a Rosner correction index of

less than 12%. She had no excessive bleeding during or after the procedure and had no thromboembolic events during or after her hospital stay. She was seen a month later in the outpatient clinic where she was well and asymptomatic. She was given an appointment in another month to review her factor assay results however she was lost to follow up. The factor study revealed a Factor XII deficiency.

9 months later, she was referred back by the community health clinic to the hospital when she was in her 4th pregnancy at 37 weeks. According to the health clinic, her pregnancy has been progressing well. She was electively admitted after the hospital clinic review for caesarean section. She was observed postnatally for four days during which period she was well. The results of her investigations and coagulation factor activity results are shown in table I and II respectively.

Table II: Coagulation factor activity (14/02/2018)

	Value	Normal Range
Prothrombin Time	11.4 sec	9-12sec
APTT	180.0sec	26-38sec
Fibrinogen concentration	401 mg/dl	150-450 mg/dl
D – dimer	-- ug/dl	<25ug/dl
Sample appearance	Clear	
Clot Retraction	-	
Clot-Stability Test FX111	-	
Bleeding Time (Duke's)	-	<3.0min
Factor V111:C Activity	57.6 %	50-150%
Factor IX:C Activity	112.9 %	50-150%
Factor XII:C Activity	0.0	
Factor IX:C Activity	112.5	

Impression
Normal PT and fibrinogen with markedly prolonged APTT.
Normal factor IX and XI. Normal factor VIII. 0% factor XII.
Diagnosis: Factor XII deficiency

DISCUSSION

Factor XII was previously associated with thrombosis since the death of John Hageman due to pulmonary thromboembolism. However, recent papers have questioned this risk of thrombosis as no causal relationship has been established so far (2). Factor XII is a plasma protein produced in the liver and plays its role in coagulation via the intrinsic pathway. Factor XII deficiency is inherited as an autosomal recessive trait (3). The prevalence of this deficiency is reported to be 1.5 – 3% among the Western population (4). There is no data as to the prevalence or incidence of Factor XII deficiency in South-East Asian or Malaysian population.

Even though factor XII is initially thought to be needed in ensuring proper blood clotting in the body, however, whenever there is a deficient state, other blood clotting factors will take shape and compensate for its absence. Therefore, the disorder is considered to be benign and usually is only detected by chance during routine pre-operative blood tests.

Fetal loss in early pregnancy is contributed to by numerous factors including an imbalance in the clotting system such as thrombosis leading to placental insufficiency. A study was done by Ozgu-Erdinc AS et al. has shown that factor deficiency was associated with recurrent miscarriages (3). In this study, the author had studied 1257 women with a history of recurrent miscarriages and found that Factor XII deficiency was present in 7.4% of the women. Unfortunately, the author did not carry out any thrombophilic screen for the subjects. Without such data, it is difficult to make any concrete conclusion regarding the true link of Factor XII deficiency and miscarriage.

The relationship between Factor XII and pregnancy loss is ambiguous as studies have shown both positive and negative associations. The uncertainty is likely

Table I: Investigation results

Date	02/01/2018	03/01/2018	14/02/2018	07/12/2018	14/12/2018
PT (sec)	13.1 sec	14.3 sec		12.0 sec	12.5 sec
INR	0.98	1.1		0.95	0.95
APTT (sec)	78.1 sec	110 sec		150 sec	89 sec
Anticardiolipin antibodies			Negative		
Anti Beta 2 glycoprotein – 1			Negative		
Lupus anticoagulant			Negative		
Protein C, S			Normal		
APTT		86.7 sec			
APTT Control		33.8 sec			
Immediate mixing		35.8 sec			
2 hours incubation mixing		37.9 sec			
Rosner Index Immediate mixing		2.31%			
2 hours incubation mixing		4.73%			

Rosner Index (Index of correction): * <12 Correction (suspicion - factor deficiency)

contributed to multiple factors. Recurrent abortions have multiple known causes, which include chromosomal, endocrinologic, immunologic, anatomical, and exogenous factors. Disturbances in coagulation and fibrinolytic system may lead to recurrent abortions if we hold to the theory that recurrent abortions are mostly thrombotic in nature. Thrombophilia has many causative aetiologies and it could be inherited or acquired in conditions such as prolonged immobilization, pregnancy, use of oral contraceptives, or smoking. These risk factors must be considered when estimating individual risk in a patient with recurrent abortion.

In our case, the finding of Factor XII was purely by chance. We had initially investigated this lady for the prolonged APTT with a history of miscarriages with a mixing test as she was suspected to have antiphospholipid syndrome. However, the mixing test and subsequent factors analysis revealed a Factor XII deficiency. She had two completely uneventful pregnancies which she managed to complete till delivery with no complications antenatally or postnatally. This corresponds to other case reports in which patients have also had completed pregnancies without any complications or factor replacement (2,5).

CONCLUSION

Thus, we report an incidental finding case of Factor XII deficiency with normal pregnancy and puerperium. Due to its rarity of occurrence in the general population, we hope that our case report can further enrich our understanding of this rare disease.

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