Hereditary factor XII deficiency in an adult patient: A case report

Rehab Y Al-Ansari¹, Fatimah Al-Yami², Ghayah Almulhim³ and Alexander Woodman⁴

Abstract
Factor XII deficiency is a rare autosomal recessive health condition usually discovered incidentally during routine coagulation screening before surgery after investigating a prolongation of the activated partial thromboplastin time. This is a case of a 29-year-old man from Saudi Arabia who was selectively admitted to the surgical department to treat a perianal fistula and found incidentally prolonged activated partial thromboplastin time and factor XII deficiency. Examination of the skin revealed no bruising, petechiae, or ecchymosis. Systemic examination was normal. Laboratory examination showed an activated partial thromboplastin time > 160 s (normal between 27 and 38), which was repeated twice with low factor XII < 5.7% (73–121). Other factors and the work of hemostasis were within the normal range. Surgery was delayed at the request of the patient. One year later, the patient was admitted to the clinic after surgery without bleeding and did not require factor correction before or after surgery. However, treating factor XII–deficient patients specifically for preoperative preparation is challenging. Therefore, this rare case should be recorded and reported the same way as a number of previously rarely reported cases.

Keywords
Bleeding disorder, coagulation factor, factor XII deficiency, fresh frozen plasma, partial thromboplastin time

Introduction
Factor XII (FXII) is an essential physiological mediator of hemostasis, inflammation, the complement system, and fibrinolysis.¹⁻³ FXII is required for a normal result on surface-activated coagulation tests to diagnose possible coagulation factor deficiencies.⁴⁻⁶ First described by Davie and Ratnoff in 1955, FXII deficiency, also known as the Hageman factor, is one of the rare abnormal in vitro coagulation defects that can be hereditary (i.e. autosomal recessive) or acquired.²⁻⁴ The causes of acquired XII deficiency include nephrotic syndrome, sepsis, and disseminated intravascular coagulation. The incidence of FXII deficiency is relatively low at 1 in 1,000,000 people.⁴ FXII is typically diagnosed incidentally when an isolated prolonged activated partial thromboplastin time (aPTT) is observed during preoperative evaluation.¹⁻³

It has been argued that FXII deficiency may lead to thromboembolic complications.⁵⁻⁶ However, this argument is considered contradictory as FXII deficiency is not evidently associated with any risk of bleeding, nor is it protective against thrombosis. Thus, often, even after major surgery or injury, people with FXII deficiency do not experience excessive bleeding. The ongoing arguments about whether partial FXII deficiency is a risk factor for thrombosis remain unresolved.⁷⁻⁹ Nevertheless, risk management is required to improve treatment and prevent possible complications in people with FXII deficiency. In addition, due to the rarity of cases, FXII deficiency is a subject of ongoing research, whereas each case is considered unique.⁶⁻⁹

This study reports the case of a 29-year-old man from Saudi Arabia who was selectively admitted to the surgical...
department to treat a perianal fistula and found incidentally with prolonged aPTT and FXII deficiency.

Case report

A 29-year-old man from Saudi Arabia, hospitalized in the surgical department for the treatment of perianal fistula, was examined by a hematologist for consultation regarding the incidental finding of an aPTT. The patient had no prior tendency to bleed or bruise and stated no family history of coagulation factor deficiencies. A genetic test was not conducted due to the absence of subsequent complaints from the patient. However, no clear acquired causes were identified either.

Joint pain or swelling was denied. No history of thrombosis of any location. On examination, vital signs were normal: blood pressure 127/85 mm Hg, temperature 36.7°C, pulse 88 beats/min. There were no significant gastrointestinal disturbances, apart from the presence of a perianal fistula and fissure. Cardiovascular, respiratory examination, and musculoskeletal and central nervous system examination revealed within normal range results. Skin showed no hypo-, hyperpigmentation, or bruising.

Laboratory tests showed a hemoglobin of 15.2 g/dL, a platelet count of $44 \times 10^3 \text{ul.}$, and a white blood cell count of $4.44 \times 10^3 \text{ul.}$ aPTT > 160 s (normal between 27 and 38) twice, prothrombin time (PT) 11.7 s (10.9–13.6), and international normalized ratio (INR) 1.0 IU (normal 0.8–1). aPTT corrected to 34.4 s after mixing 50:50 patient plasma to normal normalized ratio (INR) 1.0 IU, and aPTT was associated with FXII deficiency. Prolonged aPTT may also suggest the presence of an inhibitor, which may be specific, such as anticoagulant therapy or liver disease.

This report presented a patient’s case where the FXII deficiency was found incidentally during routine preoperative tests. This was consistent with an earlier retrospective study among n=115 Saudi patients who were incidentally diagnosed with silent FXII deficiency during preoperative routine blood tests. The authors concluded that FXII deficiency is prevalent in the asymptomatic population of Saudi Arabia. They further recommended that FXII deficiency be routinely evaluated in patients undergoing surgery to avoid health complications during the postoperative period.

Laboratory hemostatic tests, and liver and kidney values were within normal limits. In addition, the patient in this study refused FFP transfusion to correct aPTT and FXII before surgery due to social reasons. Instead, a year later, he went to a hematologist clinic to monitor FXII deficiency. As a result, without complaints, bleeding, and the need for preoperative transfusion of blood products or replacement therapy, three perianal fistulas, and two local abscess drainages were placed in him. This finding was consistent with an earlier argument by Key who suggested that FXII is clearly not associated with any risk thrombosis or coagulation factor deficiencies.

In sum, while there is a reasonable agreement in the data linking FXI deficiency with hemostatic or thrombotic disorders, the same cannot be concluded for FXII. Thus, although FXII deficiency itself has been considered a risk factor for venous thromboembolism, re-evaluation of reported cases and extended pedigrees with FXII deficiency suggested that most affected patients had other hereditary or
acquired risk factors that were more likely to explain the thrombotic events.\textsuperscript{7,8}

In this study, the patient has not been followed up due to non-compliance with the follow-up regimen, which limited further evaluation and treatment. The family screening was not performed as the patient had no subsequent complaints. However, family screening is recommended in future studies, given the rarity of FXII deficiency and the importance of facts in such cases.

**Conclusion**

The current case report showed the patient with prolonged aPTT and FXII deficiency without complaints and the need for preoperative transfusion of blood products or replacement therapy underwent three perianal fistulas and two local abscess drainages were placed. Treatment of patients with FXII deficiency specifically for preoperative preparation is difficult due to the rare cases. It is important to consider that using a plasma product or FXII replacement should only be undertaken after carefully considering all possible outcome measures. Data of these cases are recommended to be recorded and reported to enrich clinical practice data.

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**Ethical approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed consent**

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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**ORCID ID**

Rehab Y Al-Ansari \(\text{ID}\) https://orcid.org/0000-0003-4331-5769

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