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CASE REPORT

A Case Report of Coagulation Factor XII Deficiency

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SUMMARY

Background: **Coagulation factor XII (FXII) deficiency is a rare coagulation disorder, often incidentally detected during routine physical examinations, invasive procedures, or preoperative screenings, with no specific clinical manifestations. Here, we report a case of FXII deficiency.**
Methods: **A 46-year-old female patient was found to have unexplained prolonged activated partial thromboplastin time (APTT) during routine preoperative testing, without clinical bleeding symptoms. We performed an APTT mixing study, anti-cardiolipin antibody (ACA) testing, anti-β2-glycoprotein 1 (anti-β2-GP1) antibody testing, lupus anticoagulant (LA) screening, and coagulation factor assays to determine the cause of APTT prolongation.**
Results: **The APTT mixing study showed correction result. Coagulation factor assays revealed significantly reduced FXII activity (0.1%), while factors XI, X, II, VIII, IX, V, and VII levels were elevated. ACA (IgA/IgG/IgM) and anti-β2-GP1 antibodies (IgA/IgG/IgM) were negative. LA testing by dilute Russell's viper venom time (dRVVT) was negative, and the silica clotting time (SCT) suggested factor deficiency rather than an inhibitor. These findings confirmed that the patient's prolonged APTT was due to FXII deficiency.**
Conclusions: **When prolonged APTT is observed in a patient without bleeding symptoms, laboratory personnel should consider the possibility of FXII deficiency.**
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KEYWORDS

coagulation factor XII, deficiency, hemorrhage, thrombosis

INTRODUCTION

Coagulation factor XII (FXII) deficiency is a rare coagulation disorder that can be classified as hereditary or acquired. Most cases are hereditary, associated with chromosomal abnormalities caused by mutations in the F12 gene, whereas acquired deficiency usually has identifiable underlying conditions (e.g., pregnancy, liver transplantation) [1]. Both hereditary and acquired FXII deficiency lack specific clinical manifestations. Laboratory testing typically reveals only prolonged activated partial thromboplastin time (APTT), and the condition is often incidentally detected during physical examinations, before invasive procedures, or in preoperative screenings [2]. This article reports the clinical data and laboratory findings of a patient with FXII deficiency to provide a reference for the diagnosis and management

Table 1. The results of the patient's APTT mixing study.

Test Items	Results
APTT1 (patient)	156.5 seconds
APTT2 (normal pooled plasma)	25.4 seconds
APTT3 (1:1 mixed plasma for immediate testing)	33.2 seconds
APTT4 (the patient plasma was incubated for 2 hours)	167.5 seconds
APTT5 (normal pooled plasma was incubated for 2 hours)	29.0 seconds
APTT6 (1:1 mixed plasma was incubated for 2 hours)	41.1 seconds
APTT7 (plasma was 1:1 mix after 2 hours of incubation respectively)	40.5 seconds
Rosner Index (RI instantly)	5.0%
Rosner Index (RI incubated for 2 hours)	6.9%

Normal pooled plasma from 20 healthy donors was mixed with the patient's plasma 1:1, and the APTT was measured immediately after mixing (the APTT value was recorded immediately after the 1:1 mixture), and then the APTT was measured again after 37°C water bath incubation for 2 hours to observe whether the test results of the mixed plasma were corrected. Whether the correction is measured by the Rosner Index (RI). RI = [(1:1 Mixed APTT - NPP APTT)/Patient APTT] x 100%, if RI value < 10%, the result is corrected, indicating that the coagulation factor is deficient. If the RI > 15%, the result is uncorrected, indicating the presence of coagulation inhibitors, and 10% - 15% is the cutoff value (gray zone).

of this deficiency.

CASE REPORT

A 46-year-old female patient was admitted on June 25, 2022, for "uterine fibroids" diagnosed by outpatient ultrasound on June 6, 2022.

Patient admission coagulation tests revealed: PT: 10.1 seconds (reference range: 8.3 - 14.3 seconds), APTT: 156.5 seconds (reference range: 22.0 - 32.0 seconds), Fibrinogen: 1.75 g/L (reference range: 1.8 - 3.5 g/L), Thrombin Time: 19.2 seconds (reference range: 15.2 - 21.2 seconds), D-dimer: 0.27 mg/L FEU (reference range: 0 - 0.55 mg/L).

The coagulation tests revealed a significantly prolonged APTT (156.5 seconds), while all other routine laboratory parameters (including complete blood count, liver function, kidney function test and tumor markers) showed no clinically significant abnormalities.

What caused the markedly prolonged APTT in this patient? We first repeated the test on the same sample, obtaining consistent results with the initial measurement. Simultaneously, the internal quality control (IQC) for APTT on that day was verified to be within acceptable limits. Both the coagulation analyzer and reagents were confirmed to be suitable. Therefore, we concluded the test results were reliable. After consulting with the clinical team, we confirmed the patient had no clinical bleeding symptoms and no history of anticoagulant medication use (e.g., heparin).

To further investigate the underlying cause of the prolonged APTT, we immediately initiated an APTT mixing study following our department's standardized protocol for abnormal coagulation results [3]. The correction observed in both immediate and incubated mixing studies (RI consistently < 10%) indicates this APTT prolongation was caused by intrinsic pathway coagulation factor deficiency (Table 1).

We performed pathologic anticoagulant screening for the patient. Anti-cardiolipin antibodies (IgA/IgG/IgM) were negative. Anti-β2-glycoprotein 1 antibodies (IgA/IgG/IgM) were negative. Lupus anticoagulant-dRVVT ratio was 0.9 (negative). Lupus anticoagulant-SCT result indicated no clot formation (suggestive of severe factor deficiency or higher inhibitor).

Coagulation factor testing was conducted with the following findings: Factor XII: 0.1% (reference: 50 - 120%); Factor XI: 122.8% (reference: 50 - 120%); Factor IX: 121.9% (reference: 50 - 120%); Factor VIII: 191.5% (reference: 50 - 120%); Factor X: 134.7% (reference: 50 - 120%); Factor V: 138.0% (reference: 50 - 120%); Factor II: 132.8% (reference: 50 - 120%); Factor VII: 129.1% (reference: 50 - 120%).

The coagulation studies demonstrated severely reduced Factor XII activity and elevated levels of other coagulation factors. Based on these results, the patient was diagnosed with severe Factor XII deficiency.

The patient successfully underwent laparoscopic myomectomy under general anesthesia on July 4, 2022. No intraoperative bleeding complications and normal postoperative recovery were observed.

DISCUSSION

The APTT test is highly sensitive to deficiencies in intrinsic pathway coagulation factors (e.g., FVIII, FIX, FXI, FXII) and serves as the most common screening assay for the intrinsic coagulation system.

This case was found to have abnormal coagulation parameters during preoperative screening, characterized by isolated, markedly prolonged APTT. Given that distinct pathophysiological mechanisms underlie intrinsic pathway abnormalities, each requiring specific clinical management, the key was to determine the precise etiology of APTT prolongation. The APTT mixing study is a simple and effective coagulation test for the initial identification of the cause of APTT prolongation, and the RI results of the immediate and 2-hour incubated APTT correction in this case were < 10%, indicating that the case had APTT prolongation caused by the lack of intrinsic pathway coagulation factors. The results of the subsequent coagulation FXII factor activity test were 0.1%. In addition, the pathological anticoagulant

test dRVVT was negative, and the SCT test results indicate factor deficiency or the presence of factor antibodies. Thus, the patient was diagnosed with severe Factor XII deficiency.

Coagulation factor XII, also known as Hageman factor, was first reported by Ratnoff et al. in 1955 [4]. FXII deficiency is a rare coagulation disorder. Exact prevalence of this condition is not known, as under normal conditions it is asymptomatic [5]. There is no obvious absence of bleeding manifestations in clinical practice, only APTT prolongation, and most of them are preoperative, invasive or incidental findings on physical examination. Evidence demonstrates the intrinsic pathway of coagulation is initiated by FXII through contact with negatively charged surfaces that induces a conformational change in zymogen FXII. A small amount of activated FXII (FXIIa) activates plasma prekallikrein into kallikrein, which in turn reciprocally activates more FXII. FXIIa also activates factor XI, which activates factor IX and then goes through the intrinsic pathway. In hemostasis, this process may be redundant as factor IX can be activated by tissue factor VIIa complex without factor XI or XII, while factor XI can also be activated by thrombin without FXII. This explains why FXII deficiency does not lead to clinically significant bleeding symptoms [6,7]. Therefore, although the activity of FXII in this case was very low, it did not affect her normal surgery, and the patient had optimal recovery after surgery.

In vitro coagulation assays, such as the APTT, cannot fully replicate the complex hemostatic balance *in vivo*. The APTT is specifically designed to initiate clotting through the FXII-dependent contact activation pathway. Consequently, FXII deficiency invariably results in a markedly prolonged APTT. It is critical to distinguish this from other causes of APTT prolongation, such as deficiencies in factors like VIII or IX, or the presence of lupus anticoagulant, as the underlying mechanisms and corresponding clinical management differ significantly. Therefore, determining the precise etiology of a prolonged APTT is a prerequisite for initiating appropriate and targeted clinical management.

Declaration of Interest:
None.

References:

1. Jiang S, Chen Y, Xie H, Liu M, Zheng X, Wang M. A Novel Homozygous Missense Mutation (Ile583Asn) in a Consanguineous Marriage Family with Hereditary Factor XII Deficiency: A Case Report. Hamostaseologie 2023 Apr;43(2):142-5. (PMID: 36481867)

2. Aljabry M, Algazlan A, Alsubaie N, Dher SB, Aljabri HS, Alotaibi GS. Homozygous missense variant F12 (Gly506Asp) associated with severe factor XII deficiency: a case report. J Med Case Rep 2023 Dec 7;17(1):504. (PMID: 38057855)

3. Favaloro EJ. Coagulation mixing studies: Utility, algorithmic strategies and limitations for lupus anticoagulant testing or follow up of abnormal coagulation tests. Am J Hematol 2020 Jan;95(1): 117-28. (PMID: 31674066)

4. Yoshida K, Tanaka S, Sato Y, Watanabe K, Muramatsu K, Murakawa M. Global cerebral infarction after aortic arch replacement surgery in a patient with postoperatively revealed factor XII deficiency: a case report. J Med Case Rep 2020 Sep 11;14(1):150. (PMID: 32912328)

5. Chaudhry LA, El-Sadek WYM, Chaudhry GA, Al-Atawi FE. Factor XII (Hageman Factor) Deficiency: a rare harbinger of life threatening complications. Pan Afr Med J 2019 May 21;33:39. (PMID: 31384354)

6. Renne T. The procoagulant and proinflammatory plasma contact system. Semin Immunopathol 2012 Jan;34(1):31-41. (PMID: 21858560)

7. Chou SC, Lin CY, Lin HY, et al. Characterization of congenital factor XII deficiency in Taiwanese patients: identification of one novel and one common mutation. Int J Hematol 2022 Oct;116(4): 528-33. (PMID: 35675023)