

Prolonged Activated Partial Thromboplastin Time: A Case Report

Gaćina, Petar; Čaržavec, Dubravka; Raić, Biserka; Stančić, Vladimir

Source / Izvornik: **Acta clinica Croatica, 2005, 44, 385 - 388**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:220:308114>

Rights / Prava: [Attribution-NonCommercial-NoDerivatives 4.0 International/Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2025-02-23**



Repository / Repozitorij:

[Repository of the Sestre milosrdnice University Hospital Center - KBCSM Repository](#)

PROLONGED ACTIVATED PARTIAL THROMBOPLASTIN TIME: A CASE REPORT

Petar Gaćina, Dubravka Čaržavec, Biserka Raić and Vladimir Stančić

Department of Hematology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY—A case of a 75-year-old female referred to our hospital for hip replacement with preoperative laboratory test of prolonged activated partial thromboplastin time due to factor XII deficiency is described. Other coagulation parameters known to be associated with prolonged activated partial thromboplastin time like factor VIII, factor IX, factor XI, high-molecular-weight kininogen and prekallikrein were normal, and there was no evidence for the presence of unspecified circulating anticoagulants or heparin. There is a general consensus that factor XII deficiency usually does not result in hemorrhagic diathesis. Its relationship with overt venous thrombosis is still unclear. The patient and her family had no history of bleeding disorder or thromboembolic events. There were no excessive bleeding or thromboembolic incident during the surgery and postoperative recovery.

Key words: *Factor XII deficiency – etiology; Factor XII deficiency – complications; Factor XII deficiency – genetics; Blood coagulation disorders – complications*

Introduction

Isolated prolongation of activated partial thromboplastin time (aPTT) is suggestive of deficiency of either factor VIII, factor IX, factor XI, factor XII, prekallikrein, high-molecular-weight kininogen, presence of heparin, lupus anticoagulants or specific inhibitors, and high hematocrit (>60%).

Factor XII (F XII) is an activator of both intrinsic blood coagulation system and kinin system. It is a single chain glycoprotein synthesized in the liver that circulates as an inactive zymogen. During contact activation, F XII is proteolytically cleaved at several sites by plasma kallikrein to yield enzymatically active F XIIa. Factor XIIa is capable of activating prekallikrein and factor XI. Moreover, F XII seems to be capable of autoactivation. The major plasma protease inhibitor of activated F XIIa is C1 inhibitor. More than 90% of the inhibition of these proteases in plasma is attributed to this

serpin. Endothelial cells produce a protein that inhibits activation of F XII but not F XIIa proteolytic activity¹. There is also reasonable evidence to suggest that F XII and other contact factors (prekallikrein and high-molecular-weight kininogen) play a role in host defense mechanisms and may contribute to the interaction between coagulation, fibrinolysis, the complement system, and other pathways of the inflammatory response².

F XII concentration in plasma is $31 \pm 8 \mu\text{g per mL}^3$. Its biological half life is 50-70 hours. In general, congenital F XII deficiency is inherited in an autosomal recessive pattern, although autosomal dominant inheritance has been described in one family⁴. Homozygous individuals usually have undetectable F XII activity levels, while heterozygotes have F XII levels between 20% and 60% of normal. Congenital deficiency of F XII has been described in an individual with von Willebrand's disease⁵, another one with factor IX deficiency⁶, and a carrier of hemophilia B who also had von Willebrand disease⁷. F XII deficiency may also be an acquired disorder. Postmenopausal women treated with estrogens and pregnant women have elevated plasma levels of F XII expression. Levels of F XII and factor XI are slightly decreased in advanced liver disease and hepatitis but

Correspondence to: *Petar Gaćina, M.D.*, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: petar.gacina @ zg.htnet.hr

Received September 30, 2005, accepted November 21, 2005

are normal or increased in obstructive jaundice⁸. These subtle changes do not play a role in bleeding episodes of advanced liver dysfunction. Rarely, F XII deficiency results from spontaneous development of an antibody (i.e. inhibitor) to F XII⁹. Such inhibitors have been identified in individuals treated with phenothiazines, chlorpromazine and procainamide, or in patients with autoimmune disorders^{10,11}. The Asian population seems to have lower F XII levels when compared to Caucasians¹². F XII deficiency is not associated with a bleeding tendency, while its relationship with overt venous thrombosis is still unclear.

Some cases of F XII deficiency result from deficient or absent synthesis of the F XII molecule; others result from the synthesis of an abnormal molecule¹³. The amino acid sequence of F XII was determined by Edman degradation in 1985. The F XII gene is located on chromosome 5q 33-qter¹⁴.

The first case of congenital F XII deficiency was identified in 1955 by Ratnoff and Colopy¹⁵ in an individual named John Hageman during routine preoperative testing. He had no personal or family history of excessive bleeding. His plasma showed a prolonged clotting time, not explained by the then known coagulation factor deficiencies. The missing plasma protein has become known as Hageman factor or coagulation F XII¹⁶. Since then, several hundred other individuals have been described, however, structural defect in F XII has only been recognized in a few of these cases. The characteristic of severe F XII deficiency is a markedly prolonged aPTT (> 100 seconds). The other coagulation screening tests (prothrombin time, thrombin time, and bleeding time) are normal. Diagnosis requires a specific F XII assay¹⁷.

Generally, no specific therapy is required for individuals with F XII deficiency.

Case Report

A 75-year-old woman was admitted to surgery department for placement of a hip prosthesis. Results of preoperative routine laboratory tests were within the normal values except for prolonged aPTT. A detailed investigation of hemostasis was performed. The only pathologic finding was a significant reduction in F XII activity (16%; normal range 70%-120%). Other factors known to be associated with prolonged aPTT like factor VIII, factor IX, factor XI, prekallikrein, and high-molecular-weight kininogen were normal. There was no

evidence for the presence of unspecified circulating anticoagulants, antibodies to F XII, or heparin. We concluded that the lack of F XII was the cause of prolonged aPTT. She and her family had no history of bleeding disorders or thromboembolic events. We started with preoperative heparin thromboprophylaxis, as specified by the accepted procedures, and continued it after the surgery. There was no excessive bleeding or thromboembolic incident during the surgery or postoperative recovery.

Discussion

Subjects with F XII deficiency, even those with undetectable activity, do not exhibit bleeding diathesis. Although F XII is necessary for *in vitro* coagulation during aPTT testing, its presence seems to be irrelevant for *in vivo* hemostasis. Even a major surgery can be performed in individuals with F XII deficiency without hemorrhagic complications. Therefore, transfusion with fresh frozen plasma or cryoprecipitate for the correction of low F XII plasma concentration in patients with isolated severe F XII deficiency is not justified. In fact, the original patient in whom this disorder was defined died of pulmonary embolism probably because of concomitant prothrombotic conditions (fractured hemipelvis and subsequent bedrest). Various anecdotal case reports describe an association between F XII deficiency and arterial or venous thromboses, pulmonary embolism, myocardial infarction, spontaneous abortion, and premature delivery, but a definite cause-and-effect relationship has not been established¹⁸⁻²¹. In some cases this thrombophilic tendency has been attributed to a reduced plasma fibrinolytic activity²². Yet, some controversy remains and the results of other studies claim this is not the case²³⁻²⁵. Thus, it remains unproven if F XII deficiency is associated with an increased risk of thrombosis.

Hip surgery for either fractured hip or total hip replacement has always been an operation fraught with thromboembolism, which is the major cause of death in these patients. F XII deficient patients may have additional hypercoagulability through defective activation of fibrinolysis. So, these patients have a moderately increased thromboembolic risk during surgery and necessitate use of heparin thromboprophylaxis and early mobilization without plasma replacement therapy.

Our patient with F XII deficiency received preoperative and postoperative heparin and later warfarin throm-

boprophylaxis, and there were no unexpected bleeding episodes or thromboembolic complications during the surgery or postoperative period.

These data provide further evidence that F XII deficiency does not only show any bleeding tendency but can also withstand even major surgical procedures without thrombotic complications.

References

1. KLENIEWSKI J, DONALDSON VH. Endothelial cells produce a substance that inhibits contact activation of coagulation by blocking the activation of Hageman factor. *Proc Natl Acad Sci USA* 1993;90:198-202.
2. COLMAN RW. Biologic activities of the contact factors in *in vivo* – potentiation of hypotension, inflammation, and fibrinolysis, and inhibition of cell adhesion, angiogenesis and thrombosis. *Thromb Haemost* 1999;82:1568-77.
3. KESSLER C. Coagulation factor deficiencies. In: GOLDMAN L, ed. *Cecil textbook of medicine*, 21st ed. Philadelphia, USA: WB Saunders Company, 2000:1004-12.
4. BENNETT B, RATNOFF OD, HOLT JB, ROBERTS HR. Hageman trait (factor XII deficiency): a probably second genotype inherited as an autosomal dominant characteristic. *Blood* 1972;40:412-5.
5. BUX-GEWEHR I, MORGENSCHWEIS K, ZOTZ RB, *et al.* Combined von Willebrand factor deficiency and factor XII deficiency. *Thromb Haemost* 2000;83:514-6.
6. MANT MJ. Combined factor IX and XII deficiencies in both male and female members of a single family. *Thromb Haemost* 1979;42:816-8.
7. BEARD J, DUDLEY JM, HOLLAND LJ, LAWRIE A, SAVIDGE GF. Combined von Willebrand's disease and factor XII deficiency in a carrier of haemophilia B. *Clin Lab Haematol* 1989;11:139-41.
8. LECHNER K, NIESSNER H, THALER E. Coagulation abnormalities in liver disease. *Semin Thromb Hemost* 1977;4:40-56.
9. CRIEL A, COLLEN D, MASSON PL. A case of IgM antibodies which inhibit the contact activation of blood coagulation. *Thromb Res* 1978;12:883-92.
10. CLYNE LP, FARBER LR, CHOPYK RL. Procainamide-induced circulating anticoagulants in a congenitally-defective factor XI patient. *Folia Haematol Int Mag Klin Morphol Blutforsch* 1989;116:239-44.
11. ZUCKER S, ZARRABI MH, ROMANO GS, MILLER F. IgM inhibitors of the contact activation phase of coagulation in chlorpromazine treated patients. *Br J Haematol* 1978;40:447-57.
12. GORDON EM, DONALDSON VH, SAITO H, *et al.* Reduced titers of Hageman factor (factor XII) in Orientals. *Ann Intern Med* 1981;95:697-700.
13. SAITO H, SCOTT JG, MOVAT MZ, *et al.* Molecular heterogeneity of Hageman trait (factor XII deficiency): evidence that 2 of 49 cases are cross reacting material positive (CRM+). *J Lab Clin Med* 1979;94:256-65.
14. COOL DE, MacGILLIVRAY RT. Characterization of the human blood coagulation factor XII gene. Intron/exon gene organization and analysis of the 5'-flanking region. *J Biol Chem* 1987;262:13662-73.
15. RATNOFF OD, COLOPY JE. Familial hemorrhagic trait associated with deficiency of clot-promoting fraction of plasma. *J Clin Invest* 1955;34:602-13.
16. RATNOFF OD, COLOPY JE. Biology and pathology of initial stages of blood coagulation. *Prog Hematol* 1966;5:204-45.
17. KLUFT C, SVENDSEN L, LOS P. Direct assay of factor XIIa in plasma with synthetic chromogen substrates. *Adv Exp Med Biol* 1983;156:201-4.
18. RODEGHIERO F, CASTAMAN G, RUGGERI M, *et al.* Thrombosis in subjects with homozygous and heterozygous factor XII deficiency (Letter). *Thromb Haemost* 1992;67:590.
19. MANNHALTER C, FISCHER M, HOPMEIER P, *et al.* Factor XII activity and antigen concentrations in individuals suffering from recurrent thrombosis. *Fibrinolysis* 1987;1:259-63.
20. PAUER HU, BURFEIND P, KOSTERING H, EMONS G, HINNEY B. Factor XII deficiency is strongly associated with primary recurrent abortions. *Fertil Steril* 2003;80:590-4.
21. KUHLI C, SCHARRER I, KOCH F, OHRLOFF C, HATTENBACH LO. Factor XII deficiency. A thrombophilic risk factor for retinal vein occlusion. *Am J Ophthalmol* 2005;139:459-64.
22. LODI S, ISA L, POLLINI E, *et al.* Defective intrinsic fibrinolytic activity in a patient with severe factor XII deficiency and myocardial infarction. *Scand J Haematol* 1984;33:80-2.
23. KOSTER T, ROSENDAAL FR, BRIET E, VANDENBROUCKE JP. John Hageman's factor and deep vein thrombosis: Leiden thrombophilia study. *Br J Haematol* 1994;87:422-4.
24. GIROLAMI A, RUZZON E, LOMBARDI AM, CABRIO L, RANDI ML. Thrombosis-free surgical procedures in severe (homozygote) factor XII deficiency; report of four additional cases and literature review. *Clin Appl Thromb Hemost* 2004;10:351-5.
25. GIROLAMI A, MORELLO M, GIROLAMI B, LOMBARDI AM, BERTOLO C. Myocardial infarction and arterial thrombosis in severe (homozygous) FXII deficiency: no apparent causative relation. *Clin Appl Thromb Hemost* 2005;11:49-53.

Sažetak

PRODULJENO AKTIVIRANO PARCIJALNO TROMBOPLASTINSKO VRIJEME – PRIKAZ SLUČAJA

P. Gaćina, D. Čaržavec, B. Raić i V. Stančić

Prikazan je slučaj 75-godišnje bolesnice upućene u našu bolnicu radi ugradnje umjetnog kuka s prijeoperacijskim nalazom produljenog aktiviranog parcijalnog tromboplastinskog vremena zbog nedostatka faktora XII. Drugi čimbenici koji mogu uzrokovati produljenje aktiviranog parcijalnog tromboplastinskog vremena kao faktor VIII, faktor IX, faktor XI, kininogen visoke molekularne mase i prekalikrein su bili uredni, a nije bilo znakova prisutnosti cirkulirajućih antikoagulansa niti heparina. Opći stav je da nedostatak faktora XII uglavnom ne uzrokuje krvarenje, dok je još nejasna povezanost s tromboembolijom. U bolesnice i njene obitelji nije bilo anamnestičkih podataka o poremećaju krvarenja niti tromboembolije. Za vrijeme kirurškog zahvata i u poslijeoperacijskom razdoblju nije bilo značajnog krvarenja niti tromboembolije.

Ključne riječi: Nedostatak faktora XII. – etiologija; Nedostatak faktora XII. komplikacije; Nedostatak faktora XII – genetika; Bolesti zgrušavanja – komplikacije