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PROLONGED ACTIVATED PARTIAL THROMBOPLASTIN TIME: A CASE REPORT

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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 activity[1]. 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 response[2].

F XII concentration in plasma is 31 ± 8 μg *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 family[4]. 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 disease[5], another one with factor IX deficiency[6], and a carrier of hemophilia B who also had von Willebrand disease[7]. 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

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are normal or increased in obstructive jaundice[8]. 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 XII[9]. 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 Caucasians[12]. 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 molecule[13]. The amino acid sequence of F XII was determined by Edman degradation in 1985. The F XII gene is located on chromosome 5q 33-qter[14].

The first case of congenital F XII deficiency was identified in 1955 by Ratnoff and Colopy[15] 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 XII[16]. 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 assay[17].

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 established[18-21]. In some cases this thrombophilic tendency has been attributed to a reduced plasma fibrinolytic activity[22]. Yet, some controversy remains and the results of other studies claim this is not the case[23-25]. 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.

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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*