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Case Report

A Prekallikrein Deficiency Case Report

(Saudi boy with Prekallikrein Deficiency)

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Abstract

A six years old Saudi boy was referred from ENT clinic for assessment at the Pediatric Hematology clinic. He was referred from the pre-surgery clinic on November 2012 to investigate abnormal coagulation profile. It was accidently discovered that Partial Thromboplastin Time was prolonged (PTT). It was exactly at 94 seconds (normal = 30 - 40 seconds). PTT was repeated again to exclude ''lab error''; it was 122 seconds. We assessed his condition, coagulation profile showed normal Prothrombin Time "PT" and INR (12, 1.1) respectively. Revising patient history, we have found no episodes of epistaxis, nor any skin, mucosal bleedings. There was also no history of Gastrointestinal (GI) bleeding or joint bleeding. He was not on any anticoagulation therapy. There was positive family history of consanguinity but there was no specific family history of bleeding tendency.

At first, a full work up was done for the prolonged PTT including intrinsic pathway factors; FVIII, FIX, FXI and FXII levels. All were normal except factor IX was slightly low. It was suspected initially that he has factor IX deficiency (Hemophilia B). A therapeutic trial of administering Factor IX Concentrate was performed. Unfortunately, PTT was still prolonged. We don't exactly know why did this boy initially have a low factor IX, we know that factors level are not static but dynamic and change, especially it was not free low. Contact factors deficiencies, albeit rare, are usually suspected if the intrinsic pathway factors were not deficient. In particular, Fletcher Factor Deficiency (Prekallikrein Deficiency), which is an extremely rare disorder, was suspected. It should be considered in patients who have no history of bleeding tendency who also have a prolonged aPTT.

Keywords: *aPTT; Surgery; Fletcher factor; Prekallikrein; PT; INR*

Abbreviations

PTT: Partial Thromboplastin Time; PT: Prothrombin Time; GI: Gastrointestinal; HMWK: High Molecular Weight Kininogen; ENT: Ears, Nose, And Throat "Otorhinolaryngology"; INR: International Normalized Ratio; FFP: Fresh Frozen Plasma; PKK: Prekallikrein; KK: Kallikrein; VWD: Von Willebrand Disease

Introduction

Preoperative assessment of hemostatic function is mandatory to avoid perioperative risk of bleeding [1]. History taking is an important simple primary method for screening of liability to bleed [1,2]. Preoperative screening tests including partial thromboplastin time (aPTT), prothrombin time (PT), bleeding time, and platelet count. These investigations are regarded as first line investigations that should be done preoperatively. A Prolonged aPTT is a commonly encountered laboratory test result. If isolated aPTT prolongation is found then it may indicate the presence of Intrinsic Factor Deficiencies or Antiphospholipid antibodies. Other less common causes are contact factors deficiencies, namely, FXII, Prekallikrein, and High Molecular Weight Kininogen (HMWK) [3].

Case Presentation

A six years old Saudi male patient referred from Otorhinolaryngology (ENT) Pre- surgical assessment clinic on November 7, 2012. The referral was a consultation to investigate abnormal bleeding test. He was found to have a prolonged PTT. It was found to be 94 seconds (normal = 30 - 40 seconds). PTT was repeated again to exclude ''lab error''; and it was 122 seconds. Reviewing coagulation profile showed normal PT and INR (12, 1.1 respectively). Revising patient's history found no episodes of epistaxis, skin or mucosal bleeding. There was also no gastrointestinal bleeding or joint bleeding. He was not on any anticoagulation therapy. There was positive family history of consanguinity. Clearly, there was no family history of bleeding tendency. Physical examinations at all patient's visits were all unremarkable.

At first, full investigations work up was done; including factors VIII, IX, XI and XII levels. All were normal except factor IX that was slightly low. First FIX concentration was 38 % (normal range 70 - 120 %). Therefore, it was initially suspected to be factor IX deficiency (Hemophilia B). A therapeutic trial of administering factor IX was started. Unfortunately, PTT was still prolonged. Further testing of FIX concentrations were within normal values, we don't exactly know why did this boy initially have a low factor IX, we know that factors level are not static but dynamic and change, especially it was not free low.

Family was offered two options; first, giving fresh frozen plasma (FFP) and proceeding with surgery. Second, awaiting completion of laboratory investigations of intrinsic and contact factors. Family chose postponing the surgery at that time for one month, completing hematology workup and then proceeding to surgery there after.

After one month, the patient underwent the afore mentioned surgery after receiving fresh frozen plasma because there are case reports of bleeding associated with PK deficinency and the other reason it was almost impossible for anesthesia to approve giving the patient general anesthesia with prolonged and un corrected PTT. After one dose of 10 ml/kg FFP, PTT normalized immediately. The surgical procedure was devoid of any bleeding complications or healing problems. We did measure plasma Prekallikrein level (screen test) and the result was deficient, after that we did mixing study on patient's sample and it did correct at the immediate mix and after incubation, Finally, the patient was diagnosed with Prekallikrein deficiency, un fortunately we didn't analyses the PK gene because our hospital did not have resources to do.

Discussion

Prekallikrein (PKK) is a glycoprotein synthesized in hepatocytes and secreted in blood. It has a molecular weight of 88,000 Daltons as a single-chain peptide. The normal concentration is approximately 40 mg/mL [1]. Prekallikrein circulates as a complex with high-molecular weight kininogen (HMWK) in more than 70% of its mass. Less than 5% is freely circulating in plasma. The contact phase of intrinsic coagulation phase as well as fibrinolytic pathway are dependent on PK, HMWK and Hageman factor (factor XII) [2]. The activation of this phase opens the door for activation of factor XII, factor XI, and kallikrein (KK). KK is involved in many hemostatic processes such as converting Plasminogen to Plasmin, and the formation of bradykinin. It is also involved in the production of renin as well as activation of classical complement cascade pathway (Figure 1) [3].

This gene for Prekallikrein is located on the q34 - q35 region on the long arm of chromosome 4. This encoded by a single gene (KLKB1). The gene is composed of 15 exons and 14 introns [4].

Prekallikrein deficiency is a rare autosomal recessive disorder. The disease was first described in the literature by Hathaway et al in 1965. He described a prolonged aPTT in a 4 siblings. He explained that phenomenon by a 'deficiency' of undiscovered factor, which he called ''Fletcher factor''. Eight years later, Wuepper., *et al.* defined the "Fletcher factor" to be the prekallikrein [5].

The mechanism of Prekallikrein deficiency is either due to nonsense mutation, deletion or abnormal amino acid sequences. Molecular genetic analysis defined seven types of mutations. The most common mutation that often occurs in the light chain region of the gene [6].

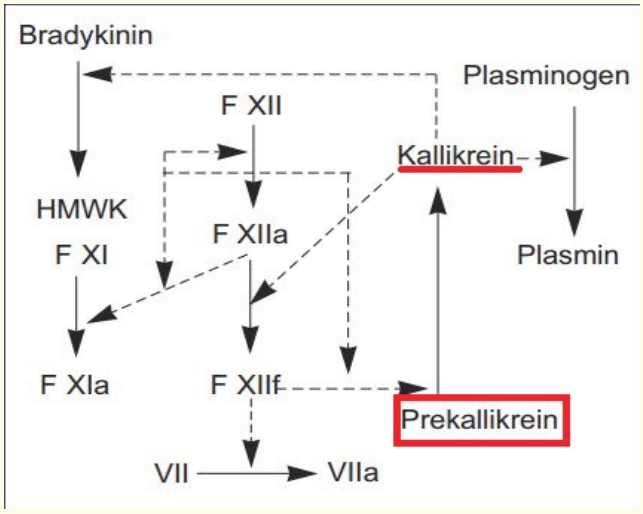

Figure 1: *Kallikrein and prekallkrein in fibrinolysis process.*

After reviewing the literatures; approximately 80 cases of this disease has been reported. The disease is mostly asymptomatic; therefore, most cases go undiagnosed unless there was a significant trauma or incidentally during the work up for surgery. The classic laboratory picture seen in patients with Prekallikrein Deficiency is a normal PT and a prolonged aPTT. Normal levels of PK, HMWK and factor XII are needed in order to maintain aPTT in the normal range. The interchangeable roles played by all contact factors explains why there is none to mild degree of bleeding tendency in all patients with PK deficiency despite a prolonged aPTT [5-7]. In additions, contact factors are not "key factors" that have essential role in the overall coagulation cascade. Their role is as an adjuvant in the generation of thrombin. Therefore, PK, HMWK and factor XII deficiencies do not cause severe bleeding diathesis. This is in part because of the fact that the activation of the target of the contact factors which is activation of factor XI is mostly mediated via platelets and thrombin [7].

Deficiencies of some coagulation factors, such as FXII, have been reported to manifest as either bleeding or thrombotic events. In addition to FXII, other factors' deficiencies, Von Willebrand disease (VWD), Hemophilia A&B, Fibrinogen, and Factor VII have been known to have this effect. Deficiency of Prekallikrein, as well as Factor II, and factor X is not associated with thrombotic events [8].

Conclusion

Prekallikrein deficiency is rare autosomal recessive disorder. It results from a mutation in gene (KLKB1) that encodes prekallikrein synthesis. Prekallikrein deficiency causes prolongation of PTT usually without any bleeding tendencies.

Conflict of Interest

There is no conflict of interests to declare regarding the publication of the paper.

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