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Saudi boy with Factor XII Deficiency

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Abstract: **Factor XII deficiency (Hageman Factor) is a very rare coagulation disorder. The role of FXII is that it acts as an activator of Factor XI. Activation of Factor XI leads to the initiation of the intrinsic pathway of the coagulation cascade. Most patients with confirmed FXII deficiency are asymptomatic. Little is known about natural history and clinical presentations of individuals affected with this rare entity. We describe a case of 2 year old girl who was referred to the pediatric hematology clinic for further investigation after she was found to have an isolated prolonged activated Partial Thromboplastin Time (aPTT). She was found incidentally after coagulation profile was performed. She was completely asymptomatic. Historically, Factor XII has been associated with thromboembolic events rather than bleeding symptoms. Majority of cases reported have no symptoms at all at time of diagnosis and no history of bleeding. Our patient was known to have a history of Developmental Dislocation of the Hip and Strabismus with past surgical history of two surgery without any bleeding complications.**

Keywords: **Prolong PPT, Factor XII.**

1. INTRODUCTION

Factor XII deficiency was first described in the medical literature in 1955 by Oscar Ratnoff and Jane Colopy in a patient named John Hageman (1). He was being screened preoperatively when he was found to have proloned activated thromboplastin time (aPTT). The disorder is sometimes named after him as Hageman factor deficiency or Hageman trait. The incidence of FXII deficiency is estimated at (1/1000,000). Over the years, FXII was found to have a minor role in bleeding tendency via activation of Factor XI by FXIIa. FXI in turn activate factor IX. The other important role that FXII has is conversion of plasminogen to plasmin, which initiates the fibrinolytic pathway. This role specifically explains the thromboembolict tendencies in individuals with FXII deficiency. (2) There are two forms of FXII deficiency: inherited and acquired. The acquired form is more associated with the thromboembolic tendencies.

2. CASE PRESENTATION

History:

2 Years old female pediatric patient attended to pediatric hematology clinic on February 2, 2015. She was being referred from orthopedic clinic after she was found to have an abnormal coagulation profile result (prolonged PTT). PTT was in the range of 60-70 seconds (normal 25-35). She has no history of bleeding even when she did two prior surgeries.

Patient has a history of Developmental Dislocation of the Hip and Strabismus. She underwent surgeries for both. There was no bleeding reported with these two procedures. She was delivered at full term (37 weeks gestational age) by caesarian section because of breech presentation. Birth weight was 2.12 kg. Mother was gravida 4, para 3, abortion 1, and living 3. Family history is positive for consanguinity and there was no history of bleeding disorders.

Physical Examination:

Vital signs were normal Height: 90.5 cm at 75th percentile. Weight was 11.4 kg at 25th percentile. Other systemic examination was unremarkable.

Investigation:

WBC: 9.3 Hb: 12Platelets: 490

PTT & PT by Date

23/12/2014: PTT: 68.6 PT: 13.2

24/12/2014: PTT: 65PT: 12.8

24/12/2014: Mixing study, PTT was 68.5 seconds. PTT after was corrected with 36.2 seconds. VWF: 97.6 IU/dl VW Ag assay: 94 IU/dl FXI: 72.4FVIII: 118FX: 91

Then we ordered Factor XI, VIII, IX, XII and made an appointment after 2 weeks.

Then in next visit mixing study showed normalization of PTT to 37, FVIII: 110, FXI : 47(normal < 50).

Then because FIX was slightly low, we suspected IX deficiency but to confirm we need to do FIX every 3 months for 6-9 months. Next visit after one week we found that IX level was 47. On subsequent analysis, FIX normalized. FXII was very low. After that gene analysis showed homozygous mutation in the locus of FXII confirming factor XII deficiency.

3. DISCUSSION

Factor XII deficiency is a rare disorder that is inherited in an autosomal recessive manner. Factor XII is one of the serine proteases. It is one of the contact factors. It is synthesized in the liver. The gene coded for factor XII is located on the tip of the long arm of chromosome 5 (7). Human Factor XII is 596 amino acids long and consists of two domains; the heavy chain (353 residues) and light chain (243 residues) held together by a disulfide bond. It is about 80,000 Daltons (5,6).

Factor XIIa activates factor XI, which in turn leads to the activation of factor IX. This is the starting point of the intrinsic pathway. FXIIa also cleaves Prekallikrein to Kallikrein؛ Kallikrein then cleaves the inactive zymogen of factor XII to yield α-FXIIa and β-FXIIa. This process leads to the activation of the intrinsic pathway and eventually the formation of the fibrin clot. Fibrin clot is then cross-linked by FXIII. Fibrin clot must be dissolved in order to have a balance between clot formation and dissociation. FXII comes again in the fibrinolytic system. The α-FXIIa cleaves prekallikrein to form kallikrein. Kallikrein cleaves the pro-urokinase to form urokinase. Urokinase activates plasminogen to plasmin which acts on fibrin to dissolve the clot (3).

Factor XII has also been used to initiate in vitro coagulation cascades in laboratory studies. Factor XII, is necessary for a normal aPTT, but its role is not crucial for normal hemostasis which is the same case as high–molecular-weight kininogen (HK), and prekallikrein (PK) (so-called contact factors) (6).

It is well-known now that deficiency of Factor XII does not cause any abnormal bleeding even after trauma or surgery. In vivo and in vitro studies showed the importance of FXII in inflammatory responses (3, 4). An experiment was done on mice models showed that a removal of factor XII does not affect hemostasis but decreased inflammatory mediators generation (6).

Factor XII deficiency is associated with an increased tendency of thrombosis in animal models as well as in humans. (6,7) So the activation of the contact factors plays a bigger role in thrombosis formation than in bleeding. The contact system usually works on the surface of endothelial cells. Kallikrein activates factor XII, which, then initiates fibrinolysis by causing activation urokinase. Therefore, activation of the contact system on cell surfaces differs mechanistically from activation on a charged surface in the aPTT. (1,9).

4. CONCLUSION

Factor XII deficiency is an extremely rare coagulation defect. It is inherited as autosomal recessive. It predisposes affected patients to thrombosis and, rarelyn, to bleeding. In a patient who has prolonged PTT with no history of abnormal bleeding even after trauma or surgery, Factor XII deficiency or other contact factor like high–molecular-weight kininogen (HK), and prekallikrein (PK) should strongly be suspected.

REFERENCES

[1] Ratnoff, O.D. and Margolius Jr., A. (1955) Hageman Trait: An Asymptomatic Disorder of Blood Coagulation. Transactions of the Association of American Physicians, 68, 149-54.

[2] Ganguli, P., Rigvardhan and Kotwal, J. (2015) Thrombosis: Presentation of a Factor XII Deficiency in 10 Months Old Child—A Rare Case. International Journal of Advances in Case Reports, 2, 708-710.

[3] Manfred Schloesser, Sacha Zeerleder, Gerd Lutze, Walter-Michael Halbmayer, Sigrun Hofferbert, Bernd Hinney, Heinz Koestering, Bernhard Lammle, Gerhard Pindur, Karsten Thies, Michael Kohler, and Wolfgang Engel, Mutations in the Human Factor XII Gene, Blood 1997 90:3967-3977

[4] Monroe DM HM, Roberts HR. Molecular Biology and Biochemistry of the Coagulation Factors and Pathways of Hemostasis. Prchal JT KK, Lichtman MA, Kipps TJ, Seligsohn U, ed. Williams Hematology. 8th ed. New York: McGraw-Hill; 2010.

[5] Beringer DX, Kroon-Batenburg LM (Feb 2013). "The structure of the FnI-EGF-like tandem domain of coagulation factor XII solved using SIRAS". Acta Crystallographica Section F. 69 (Pt 2): 94–102

[6] Wagenman BL, Townsend KT, Mathew P, Crookston KP (Jun 2009). "The laboratory approach to inherited and acquired coagulation factor deficiencies". Clinics in Laboratory Medicine. 29 (2): 229–52

[7] Renné T, Pozgajová M, Grüner S, Schuh K, Pauer HU, Burfeind P, Gailani D, Nieswandt B (Jul 2005). "Defective thrombus formation in mice lacking coagulation factor XII". The Journal of Experimental Medicine. 202 (2): 271–81.

[8] Yu H, Anderson PJ, Freedman BI, Rich SS, Bowden DW. Genomic structure of the human plasma prekallikrein gene, identification of allelic variants, and analysis in end-stage renal disease. Genomics. 2000 Oct 15. 69(2):225-34

[9] Pauer HU, Renne T, Hemmerlein B, Legler T, Fritzlar S, Adham I. Targeted deletion of murine coagulation factor XII gene-a model for contact phase activation in vivo. Thromb Haemost. 2004 Sep. 92(3):503-8

[10] Kleinschnitz C, Stoll G, Bendszus M, Schuh K, Pauer HU, Burfeind P. Targeting coagulation factor XII provides protection from pathological thrombosis in cerebral ischemia without interfering with hemostasis. J Exp Med. 2006 Mar 20. 203(3):513-8

[11] Dyerberg J, Stoffersen E. Recurrent thrombosis in a patient with factor XII deficiency. Acta Haematol. 1980. 63(5):278-82.

[12] Shariat-Madar Z, Mahdi F, Schmaier AH. Assembly and activation of the plasma kallikrein/kinin system: a new interpretation. Int Immunopharmacol. 2002 Dec. 2(13-14):1841-9.