



THROMBOSIS: PRESENTATION OF A FACTOR XII DEFICIENCY IN 10 MONTHS OLD CHILD - A RARE CASE

Prosenjit Ganguli*, Rigvardhan, Jyoti Kotwal

Department of Pathology, Army Hospital (Referral & Research), Delhi Cantt, India.

Corresponding Author:- **Prosenjit Ganguli**
E-mail: prosenjitganguli@gmail.com

<p>Article Info</p> <p>Received 26/03/2015 Revised 07/04/2015 Accepted 02/05/2015</p> <p>Key words: Thromboplastin, Venous thrombosis, Prothrombin time.</p>	<p>ABSTRACT</p> <p>Since its first discovery in 1955, coagulation factor XII deficiency was, quite surprisingly, linked with thrombosis instead of hemorrhage; indeed, John Hageman ultimately died from pulmonary embolism. After this, several reports have highlighted the association between both arterial and venous thrombosis and factor XII deficiency; however, a causal relationship is still questioned. Here, we report the case of a 10 month old male child with factor Hageman deficiency who presented with painful swelling of right lower calf. Detailed clinical examination and color Doppler confirmed venous thrombosis of right calf. There were no known predisposing factors for venous thrombosis in such a young child. Coagulation work up revealed normal prothrombin time (PT) but prolonged activated partial thromboplastin time (APTT). Keeping this in mind factor assays were performed which confirmed factor XII deficiency.</p>
--	---

INTRODUCTION

Coagulation factor XII, also called as Hageman factor, is a serine protease which is well known to be involved in hemostasis and has also been recently implicated in protein homeostasis. Factor XII is involved in the intrinsic pathway of the coagulation cascade [1]. It gets converted to its active form (activated factor XII) by limited proteolysis, either by kallikrein or by autoactivation on the surface of negatively charged compounds [2]. Activated factor XII enhances blood clotting through activation of factor XI; it also participates in the fibrinolytic pathway by activating prekallikrein in the kallikrein-kinin system and by activating plasminogen to plasmin [3]. Recently, factor XII has been identified as a key factor in the recognition of misfolded protein aggregates, extending its role beyond hemostasis [1]. The factor XII gene (*F12*) has been localized to chromosome 5q33-qter [4]. Observations that persons with factor XII deficiency are more prone to thrombotic events is a matter of ongoing debate [5].

ROLE IN THROMBOSIS

Role of actor XII deficiency in development of

thrombosis is still controversial. Recent studies with mice have greatly increased the interest in the factor XII pathway of coagulation [6]. In many murine models, thrombus formation was induced by exposing them to vascular collagen, it was shown that the inhibition or absence of factor XII had marked suppressive effect on the process of thrombosis⁷. Also, in the cerebral artery model of ischemia perfusion injury, deficiency in factor XII reduced the thrombus formation and decreased the infarction volume in cerebral vessels⁸. Interestingly, in these murine models, factor XI deficiency led to similar protection of thrombosis. It was therefore postulated that activated platelets are implicated in factor XII dependent thrombus formation [6, 7].

Platelets become activated via their GPVI immunoglobulin receptor. This signalling pathway involves ITAM containing FcR gamma chain co-receptor and activation of tyrosine kinases of Src and SyK families [6]. This causes phosphorylation and activation of protein, LAT and effectors enzyme, phospholipase Cy2 (PLCy2) [9]. It has been established in both in vivo and in vitro models that collagen induced signalling from GPVI to PLC



γ_2 plays a controlling role in flow mediated thrombus formation. This signalling causes platelet aggregation and also causes platelet procoagulant activity by the surface exposure of phosphatidylserine, which in turn provides assembly sites for coagulation factors and mediates thrombin generation [10].

A dual role of exposed collagen was also postulated in thrombus and fibrin clot formation in conditions where tissue factor was limited. Exposed collagen fibres causes platelet aggregation and in addition binds to factor XII and causes activation which in turn results in activation of other clotting factors. Positive feedback by formed thrombin enhances these reactions to produce a stable fibrin thrombus [6].

CASE REPORT

10 month old male presented with painful swelling of right lower calf. Detailed clinical examination raised suspicion for venous thrombosis of right calf. Colour Doppler was performed and venous thrombosis in right calf region was confirmed. There were no known

predisposing factors responsible for venous thrombosis in such a young child. Coagulation work up revealed normal prothrombin time (PT) but prolonged activated partial thromboplastin time (APTT). Keeping this in mind factor assays were performed. Automated coagulation analyser by Stago STA compact using functional chromogen assay was used. Principle of testing was measurement of clotting time, in the presence of cephalin and activator, of a system in which all the factors are present, constant and in excess except for the factor for which the sample is being tested. Log log graph paper was used to plot the standard Factor level (% activity) on the x-axis and their corresponding clotting times (seconds) on the Y-axis. The clotting times of the patient's plasmas and those of the controls were interpolated on this calibration lines to determine their respective factor levels (%). The results were as follows:

The child was found to be factor XII deficient. To ascertain the inheritance if any, the parents were also tested. His mother showed prolonged APTT (56 sec) and factor XII assay showed activity of 26%.

Table 1. Determination of factor level

S.No.	Test	Case	Control
1	PT	12 sec	12.5 sec
2	APTT	48 sec	38 sec
3	Factor VIII assay	72% activity	
4	Factor IX assay	60% activity	
5	Factor XI assay	72% activity	
6	Factor XII assay	31% activity	

DISCUSSION AND CONCLUSION

Gianfranco Lessiani et al [5] opened a debate with an article titled- Relationship between factor XII deficiency and thrombosis- the debate is still open?

Although majority of patients with factor XII deficiency show prolonged activated partial thromboplastin time (APTT), haemorrhagic incidents are not usually associated with the hereditary form of this factor. On the contrary, these patients suffer more often from thromboembolism as did Hageman himself [11].

We found mild to moderate deficiency of factor XII as evidenced by clotting factor assay in this case. Halbmayr et al found a surprisingly high prevalence of factor XII deficiency (20%) among patients with recurrent thromboembolism and/or myocardial infarction and 8% prevalence among patients with recurrent venous thrombosis [12]. A prevalence of 10 % among patients with venous thrombosis was reported by Mannhalter et al in 1987 [13].

In contrast, Von Kanel et al reported no significantly higher prevalence of subnormal factor XII values in thrombophilics than in healthy individual [14]. Kelleher et al found no difference in factor XII levels

between survivors of myocardial infarction and controls [15].

The conflicting reports can possibly be explained by work of Paola E et al [6]. They hypothesised that despite the role of factor XII in mouse thrombosis models, the function of human plasma XII in plasma is still a matter of debate. Several clinical studies with healthy subjects have reported that low levels of factor XII are associated with an increased risk of cardiovascular disease¹⁶. However this association was absent in subjects with factor XII level below 10 % of normal⁶. This posed a question whether low factor XII may be a cause or in fact a consequence of cardiac disease¹⁷. Yet, factor XII is indispensable for normal hemostasis.. It remains to be established conclusively as to how the thromboprotective effect of factor XII deficiency in mice translates to the human situation. On the other hand, the similarity in functions of in vitro human and mouse factor XII suggests a common contribution and or pathway to in vivo thrombus formation as well.

CONFLICT OF INTEREST

All authors have none to declare.



REFERENCES

1. Candice Y Johnson, Ashleigh Tuite, Pierre E Morange, David A. (2011). The Factor XII-4C>T variant and risk of common thrombotic disorders: A huge review and meta-analysis of evidence from observational studies. *Am J Epidemiol*, 173(2), 136-144.
2. Greer JP, Foerester J, Lukens JN et al. (2003). Wintrobe's clinical hematology. 11th edition. Philadelphia, PA: Lippincott Williams and Wilkins.
3. Schousboe I. (2008). Pharmacological regulation of factor XII activation may be a new target to control pathological coagulation. *Biochem Pharmacol*, 75(5), 1007-1013.
4. Royle NJ, Nigli M, Cool D et al. (1988). Structural gene encoding factor XII is located at 5q33-qter. *Somat Cell Mol Genet*, 14(2), 217-221.
5. Gianfranco Lessiani, Angela Falco, Elvira Nicolucci, Giancarlo Rolandi et al. (2009). Relationship between factor XII and thrombosis: the debate is still open? *J Thromb Thrombolysis*, 27, 456-457.
6. Paola EJ, van der Meijden, Imke CA Munnix, Jocelyn M Auger et al. (2009). *Blood*, 114(4), 881-890.
7. Renne T, Pozgajova M, Gruner S et al. (2005). Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med*, 202, 271-281.
8. Kleinschnitz C, Stoll G, Bendszus M et al. (2006). Targeting coagulation factor XII provides protection from pathological thrombosis in cerebral ischemia without interfering with hemostasis. *J Exp Med*, 203, 513-518.
9. Neiswandt B, Watson SP et al. (2003). Platelet collagen interaction: is GPVI the central receptor. *Blood*, 102, 449-461.
10. Heemskerk JW, Kuijpers MJ, Munnix IC, Siljander PR. (2005). Platelet collagen receptors and coagulation: a characteristic platelet response as possible target for antithrombotic treatment. *Trends Cardiovasc*, 15, 86-92.
11. Ratnoff OD, Busse RJ, Sherron R. (1968). The demise of John Hageman. *N Eng J Med*, 279, 420-423.
12. Halbmayr WM, Mannhalter C, Feichtinger C, Rubi K et al. (1992). The prevalence of factor XII deficiency in 103 orally anticoagulated outpatients suffering from recurrent venous and/or arterial thromboembolism. *Thromb Hemost*, 68, 285-290.
13. Mannhalter C, Fischer M, Hopmeier P, Deutsch E. (1987). Factor XII activity and antigen concentrations in patients suffering from recurrent thrombosis. *Fibrinolysis*, 1, 259-263.
14. Von Kanel R, Wuillemin WA, Furlan M, Lammle B. (1992). Factor XII clotting activity and antigen levels in patients with thromboembolic disease. *Blood coag fibrinol*, 3, 555-561.
15. Kelleher CC, Mitropoulos AM, Imeson J, Meade TW et al. (1992). Hageman factor and risk of myocardial infarction in middle aged men. *Atherosclerosis*, 97, 67-73.
16. Bach J, Endler G, Winkelmann BR et al. (2008). Coagulation factor XII activity, activated factor XII, distribution of factor XII c46T gene polymorphism and coronary risk. *J Throm Haemost*, 6, 291-296.
17. Kanaji T. (2008). Lower factor XII activity is a risk marker rather than a risk factor for cardiovascular disease: a rebuttal. *J Thromb Haemost*, 6, 1053-1054.

