ABSTRACT FORM ECAT SYMPOSIUM 8 – 9 NOVEMBER 2018

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Title:

Inherited FXIII deficiency: laboratory diagnosis

Abstract:

Coagulation factor XIII is a protransglutaminase that circulates in the plasma as a heterotetrameric complex of two catalytic FXIII-A-subunits and two carrier/inhibitory FXIII-B subunits ($FXIII\text{-}A_2B_2$). While practically all of the FXIII-A subunits are in complex, approximately 50% of total FXIII-B circulates in the plasma in free form. In addition to plasma, FXIII-A presents in several cell types including platelets, megakaryocytes, monocytes and monocyte derived cells as a cytoplasmic protein and composed of two A-subunits only.

During the final phase of coagulation FXIII is converted into an active transglutaminase by thrombin and calcium. Activated FXIII (FXIIIa) catalyses the formation of crosslinks between proteins through glutamyl-lysyl bonds. The haemostatic function of FXIIIa is to crosslink fibrin monomers and α2-plasmin inhibitor to fibrin. These crosslinks protect the fibrin clot from destruction by shear stress and from premature degradation by fibrinolysis. However, FXIII is a multifunctional protein; it plays important roles in several biological processes including wound healing, angiogenesis and maintaining pregnancy.

Inherited FXIII deficiency is a severe, rare (around 1 in 2 million) bleeding disorder caused by autosomal recessive mutations. The prevalence is higher in countries where consanguineous marriages are common particularly if it is combined with founder mutation. The deficiency is classified according to whether the mutation is in the *F13A1* or *F13B* gene and in either case as quantitative or qualitative deficiency. To date more than 100 different mutations in the A-subunit gene have been identified that cause FXIII deficiency. Inherited FXIII-B subunit deficiency is less common, or less commonly recognized due to its milder phenotype. In FXIII-A subunit deficiency, the A-subunit is absent or dysfunctional both in the plasma and in the platelets, while in FXIII-B deficiency the A-subunit level is significantly decreased in the plasma, but it is normal in the platelets.

FXIII deficiency is associated by severe, spontaneous bleeding, particularly in the muscles and joints. Umbilical stump bleeding is a frequent symptom and intracranial haemorrhage occurs in up to 30% of untreated patients. Other bleeding tendencies include ecchymosis, hematomas and prolonged bleeding after trauma or surgery. Women with inherited FXIII deficiency often have recurrent spontaneous miscarriages and FXIII deficiency also causes wound-healing defects.

In patients with inherited FXIII deficiency routine coagulation tests, including activated partial thromboplastin time, prothrombin time, thrombin time and other screening test of haemostasis, such as bleeding time, platelet count and platelet function tests are normal. An appropriate diagnosis is dependent both upon high clinical suspicion and FXIII-specific laboratory analysis. The International Society on Thrombosis and Haemostasis Scientific and Standardization Committee recommended an algorithm for the laboratory diagnosis and classification of the different forms of FXIII deficiency. Functional FXIII activity assays are required for the detection of the deficiency and antigen measurements are needed for its classification. Molecular genetic analysis is not essential for the diagnosis of inherited FXIII deficiency, though in countries where specific mutations are common, targeted genetic analysis might provide advantages. Advantages and limitations of the currently available FXIII assays will be discussed.