THE LABORATORY DIAGNOSIS AND CLASSIFICATION OF FACTOR XIII DEFICIENCIES

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Factor XIII (FXIII) circulates in the plasma as a tetrameric zymogen (pFXIII; FXIII-A_2B_2). Its potentially active A subunit (FXIII-A) is synthesized in cells of bone marrow origin; it is also present in platelets and monocytes/macrophages in dimeric form (FXIII-A_2). The non-catalytic B subunit (FXIII-B) is in excess and it is essential for the stabilization of FXIII-A_2 in plasmatic conditions. pFXIII is converted into an active transglutaminase (FXIIIa) by thrombin and Ca^{2+} in the terminal phase of clotting cascade. FXIIIa catalyzes an acyl transfer reaction. In the first step a peptide-bound glutamine residue forms a thioester with the active-site cysteine and ammonia is released. Then, in the second step the glutamine residue becomes covalently linked to a primary amine through isopeptide bond. If the primary amine is an ε-amino group of a peptide-bound lysine residue the end-result is the cross-linking of peptide chains. FXIIIa cross-links fibrin chains and α_2 plasmin inhibitor to fibrin. This way it mechanically stabilizes fibrin and protects it from fibrinolysis.

Inherited FXIII deficiencies are classified as FXIII-A and FXIII-B deficiencies. Deficiency of the potentially active FXIII-A is a rare (1:2,000,000), but severe hemorrhagic diathesis. Delayed umbilical stump bleeding is characteristic and in non-supplemented patients subcutaneous, intramuscular and intracranial bleeding occurs with relatively high frequency. Impaired wound healing and spontaneous abortion in women also are features of FXIII-A deficiency. Type 1 deficiency (low activity and antigen) is much more frequent than type 2 (low activity with normal or moderately decreased antigen concentration). The extremely rare B subunit (FXIII-B) deficiency (5 reported cases) results in milder bleeding symptoms. Various forms of sever acquired deficiencies due to an auto-antibody against FXIII-A have been described. Neutralizing antibodies usually inhibit FXIIIa, but interference with FXIII activation and with binding to fibrin has also been reported. In a few cases non-neutralizing anti-FXIII-A antibodies that bind to pFXIII and increase its rate of elimination from the circulation were also detected. Only a single, most recent report described severe FXIII deficiency due to an auto-antibody against FXIII-B. A significant portion of patients with an autoantibody against FXIII is suffering from autoimmune disease. Virus inactivated pFXIII concentrate is now available for treatment and prophylaxis.

A quantitative FXIII activity assay is to be used as first line (screening) test for the diagnosis of FXIII deficiency. The traditional qualitative clot solubility assay is now obsolete and should not be used as screening test. Quantitative FXIII assays are based on two principles: 1/ measurement of ammonia released during the transglutaminase reaction, 2/ the incorporation of labeled substrate amine into a glutamine donor substrate protein. The former methods are easy to perform, quick kinetic assays, while the latter ones are more sensitive, but time-consuming laborious methods. For classification FXIII-A_2B_2 antigen in the plasma is to be determined, and if it is decreased, measurement of the individual subunits in the plasma and FXIII-A in platelet lysate is recommended. Other techniques like examination of fibrin cross-linking by SDS PAGE, mixing studies and binding assays to detect neutralizing and non-neutralizing auto-antibodies against FXIII subunits are useful additions to establish the correct classification of the deficiencies, An algorithm and a scheme for the diagnosis and classification of FXIII deficiencies are presented in the lecture.