Functional Anomaly of Factor XII

J.	Justo	Aznar
P.	Piedad	Villa
A.	Amparo	Vayá
Y.	Yolanda	Mira
I.	Ignacio	Lorenzo
F.	Francisco	España

Department of Clinical Pathology, 'La Fe' Hospital, Valencia, Spain

Justo Aznar, Department of Clinical Pathology, Hospital 'La Fe', E-46009 Valencia (Spain)

In 1955, Ratnoff and Colopy [1] described a patient with a prolonged clotting time. The plasma protein missing from that patient has become known as the Hageman factor or factor XII (FXII). Since the first case, a few hundred subjects with congenital FXII deficiency have been described [2]. The majority of these subjects show a congenital lack of immuno-logically identifiable FXII, but 4 cases that have been described [3-5] had detectable amounts of nonfunctional but immunologically identifiable FXII.

In this paper, we describe a new case of abnormal FXII in a cross-reacting material-positive (CRM+) factor FXII deficiency. The subject is a 2-month-old girl who has suffered from repeated attacks of pyelonephritis since birth due to a urological malformation consisting of a double left ureter with an upper left ectopic ureter. Coagulation tests run prior to surgery revealed that the activated partial thrombin time (APTT) was longer than normal (42.6 s vs. the normal 17-25 s), but there were no other irregularities. Since this prolonged APTT was not appreciated by the doctors handling the case, the patient experienced heavy bleeding when, prior to surgery, an attempt was made to canalize a vein. A hemostasis analysis showed no anomalies in platelet number or function, fibrinolysis, von Willebrand factor or the presence of circulating inhibitors. Measurement of the intrinsic factors gave normal results, except in the case of FXII which showed activity of < 0.2%. To prepare the patient for surgery, she was given fresh plasma (10 ml/kg body weight) in order to normalize APTT levels. Surgery was then performed. No bleeding occurred either during surgery or afterwards, the child continued to receive fresh frozen plasma as substitution therapy. Table 1 gives the patient's APTT, FXIL·C and FXIL·Ag before transfusion, after the preoperative transfusion and 1 month after surgery.

Since the patients' plasma had no inhibitory effect on normal plasma APTT, the plasma did not contain circulating anticoagulants against Hageman factor.

In the patient's mother and a maternal uncle (JM) (table 2), the antigen level of Hageman factor cross-reacting protein material was

Table 1. The patient's APTT, FXIL·C and FXIL·Ag before transfusion, after the preoperative transfusion and 1 month after surgery

Date

APTT, s FXIL·C, % FXIL·Ag, %

Table 2. APTT, FXII:C and
FXIL·Ag values of the living family members of the patient's family

higher than the clotting activity. These results suggest that the patient's plasma represents a CRM+ FXII deficiency.

As in most patients with FXII coagulant deficiency, our patient was clinically asymptomatic and suffered bleeding only when subjected to surgery.

As in the case reported by Berrettini et al. [4], the plasma of two heterozygotes [4, table 2] in the patient's family contained twice as much FXII antigen as FXII activity, which indicates that the variant molecule could have been genetically determined. However, the mode of inheritance could not be established because the subject's father had normal FXII coagulant and FXII antigen values.

In the 4 cases previously described [3-5] with nonfunctional but immunologically identifiable FXII, the molecular anomaly was located in the light chain of the Hageman molecule. In 1 case [6], nonprekallikrein-activating activity was generated after cleavage of the Hageman factor molecule with trypsin. Another showed a lack of pretease activity on the kallikrein-cleaved molecule [5]. In still another case [4], the abnormal FXII molecule was very slowly activated after binding to negatively charged surfaces. In only 1 case [7] was the molecular anomaly characterized by an amino acid substitution (cys-571 Ser), possibly giving rise to an altered configuration of the enzymatic active site on the secondary substrate binding site. In the case reported here, the functional FXII anomaly has only been characterized biologically, and it has been tentatively called FXII Valencia. This case is the fifth dysfunctional FXII variant so far described. The molecular basis of this anomaly is currently being investigated in our laboratory.

346

Aznar/Villa/Vayá/Mira/Lorenzo/ España

Functional Anomaly of Factor XII

References

Ratnoff OD, Colopy JE: Familial hemorrhagic trait associated with deficiency of clot-promoting fraction of plasma. *J Clin Invest* 1955; 34:602-613.

Saito H: Contact factors in health and disease. *Semin Thromb Hemost* 1987;13:36-49. 4

Saito H, Scott G, Movat HS, Scialaja SJ: Molecular heterogeneity of Hageman trait (factor XII deficiency). Evidence that 2 of 49 subjects are cross-reacting material positive (CRM*). *J Lab Clin Med* 1979;94: 256-265.

Berrettini M, Lämmle B, Ciavarella C, Ciavarella N: Functional and immunological studies of abnormal factor XII in a cross-reacting material-positive (CRM*) factor XII deficiency (abstract). *Thromb Haemost* 1985;54:120.

Wuillemin WA, Huber I, Furland M, Lämmle B: Functional characterization of an abnormal factor XII molecule (FXII Bernn). *Blood* 1991; 78:997-1004.

Saito H, Scialla SJ: Isolation and properties of and abnormal Hageman factor (FXII) molecule in a cross-reacting material-positive Hageman-trait plasma. J Clin Invest 1981;65:1028-1035.
347