540

FIBRINOGEN GENOVA III: A NEW CONGENITAL DYSFIBRINOGENEMIA WITH BLEEDING DIATHESIS AND DEFECTIVE LYSIS BY PLASMIN. G.Castaman, F. Rodeghiero, A. Galletti, E. Barone, G. Gastaldi. Hematology Department and Hemophilia and Thrombosis Center, Vicenza and Dept. Clinical Chemistry, "Galliera" Hospital, Genova, Italy.

A new abnormal fibrinogen was recognized in a woman with lifelong bleeding symptoms. Patient's plasma exhibited prolonged thrombin and reptilase times. Very low fibrinogen level was obtained by functional assay whereas heat precipitation and immunological methods gave normal fibrinogen values. This pattern was also observed in her daughter. Patient's plasma prolonged thrombin time of normal plasma. Fibrin monomer polymerization of purified fibrinogen was severely impaired, whereas fibrinopeptide A release by thrombin occured at rate and extent indistinguishable from normal. Sialic acid content was normal. SDS-PAGE of purified molecule revealed normal pattern and factor XIII-dependent crosslinking occurred as in normal controls. Lysis by plasmin of fibrinogen examined on SDS-PAGE showed an abnormal degradation profile, only minimal traces of fragments D and E being detectable after prolonged digestion in comparison with normal. Binding of plasminogen and alfa-2-antiplasmin to fibrin was normal. This abnormal fibrinogen has been tentatively called Genova III.

541

A NEW THROMBOTIC DYSFIBRINOGENEMIA PRESENT IN SEVERAL MEMBERS OF A VENEZUELAN FAMILY. C.L. Arocha Piñango (1), A. Torres (2), R. Marchi (1), S. Rodríguez (1), H. Camarillo (2), A. Muller-Soyano (3) and N. B. Bosch (2). Instituto Venezolano de Investigaciones Científicas (1), Banco Municipal de Sangre del Distrito Federal (2) y Clínica Avila (3), CARACAS, VENEZUELA.

Up to the present, 16 dysfibrinogenemias have been described with thrombotic symptomatology, of which 3 cases showed low affinity of the fibrin for thrombin.

In this study, we describe a family with an elevated frequency of thrombotic episodes which may be due to an alteration in the fibrinogen molecule causing a defective adsorption of thrombin by the fibrin formed.

Two women, mother and daughter, were admitted to our clinic with a history of repeated pulmonary thromboembolisms. Coagulation studies (which included Antithrombin III, Protein C, etc.) revealed only a prolonged thrombin time with high fibrinogen levels (500 mg/dl) by the clot weight and immunological methods. More detailed studies on fibrinogen function showed:

1) Abnormal monomers aggregation and polymerization rate, no changes were observed in the latter when induced by reptilase followed by thrombin.
2) Normal fibrinopeptide release
3) Normal cross-linked and uncross-linked fibrin chains.
4) Low affinity of fibrin for thrombin
5) Normal plasmin degradation
6) The electron microscopy showed a normal fibrin net with the characteristic periodic cross-striations pattern but which formed more slowly than normal.

Both patients were treated with oral anticoagulants. The mother has not suffered any thromboembolic episodes in two years of treatment but the daughter has shown clinical signs of minor episodes of pulmonary thromboembolism which were confirmed by perfussion gammagraphy. In the family study, 4 members have died due to either venous or arterial thrombotic accidents. Fibrinogen function studies carried out on 8 members from 3 generations showed a prolonged thrombin time with delayed polymerization in 4 of the 8 (1 adult, 3 children), none of which have suffered any thrombotic manifestations up to the time of the study.

The name of Caracas V is proposed for this new dysfibrinogenemia.

542

FIBRINOPEPTIDE B RELEASE FROM NORMAL FIBRINOGEN AND FIBRINOGEN LONDON I IN THE PRESENCE OF INHIBITORS OF FIBRIN POLYMERIZATION. W. Ruf (1), A. Bender (1), K.T. Preissner (1), D.A. Lane (2) and G. Müller-Berghaus (1). Clinical Research Unit for Blood Coagulation and Thrombosis of the Max-Planck-Gesellschaft at the Justus-Liebig-Universität, 6300 Giessen, F.R.G. (1) and Charing Cross Hospital, London, U.K. (2).

The fibrinopeptides A and B (FPA and FPB) are cleaved from the fibrinogen molecule with different rates. In the initial phase of the thrombin-fibrinogen reaction, FPB is released with a slow rate, which is enhanced upon polymerization of desA-fibrin monomers. The aim of the present study was to further characterize the mechanism leading to the enhanced rate of FPB release during polymerization. For this purpose, the release of FPB from normal fibrinogen and from fibrinogen London I, which exhibits a polymerization defect located in the D-domain, was studied in the presence and absence of the fibrinolytic fragment D_1 (D_1) and of the synthetic tetrapeptide Gly-Pro-Arg-Pro (GPRP). Steady state parameters for fibrinopeptide release were determined under pseudo-first order reaction conditions. In the initial phase of the thrombin-fibrinogen reaction, the release of FPA was unchanged in the presence of D_1. Furthermore, the release of FPA from fibrinogen London I did not reveal any difference in comparison to normal fibrinogen. GPRP prevented not only fibrin polymerization, but also the enhanced rate of FPB release. On the contrary, the rate of FPB release in the presence of a 16- and 32-fold molar excess of D_1 over fibrinogen did not differ from a reaction mixture with no added D_1. Similiar to the inhibited rate of FPB release in the presence of GPRP, the release of FPB from fibrinogen London I occurred with a slow rate, which was not enhanced by the addition of a 16-fold molar excess of D_1. Since the release neither from normal fibrinogen nor from fibrinogen London I was affected by D_1, it was concluded that the D-E contact formed by D_1 with an E-domain of a desA-fibrin molecule does not enhance the release of FPB. While GPRP keeps fibrin in monomeric form by inhibiting the polymerization sites in the D-domains, D_1 does not prevent the formation of fibrin oligomers. Therefore, acceleration of FPB release is caused by a conformational change, which is induced by binding of reciprocal polymerization sites to an E- as well as a D-domain of the same desA-fibrin molecule.