CONCEAL, FIBRINOLYSIS AND KALLIKREIN ACTIVATION IN SEVERE INFECTIOAN AND SEPSIS: RELATION TO OUTCOME. M. Blomback (1), F. Hasebevik (2), B. Brodin (2), R. Maller (3), F. Grifhins (4) Dept. of Clinical Chemistry and Blood Coagulation, Karolinska Hospital, Stockholm, Sweden (1), Dept. of Aneumethesiology (2), and Infectious Diseases, University Hospital, Lund, Sweden (3), and National Inst Biol Standards and Control, London, UK (4).

Fetal multiple organ failure following severe infection may be related to early activation of protease cascade systems. The study aimed to relate changes in the below mentioned components to fetal multiple organ failure in 53 patients with severe infection. Half of these patients did not develop shock (group I); 12 survived septic shock (group II); and 11 died from organ failure after septic shock (group III).

To patients admitted to ICU during the first 3 days after admission, blood was sampled daily for assay of: platelet count, fibrinogen, prothrombin complex, F XII, F VIIIIC, vWF:Ag, F VII, F III, F II, Fn, TAT, D-dimer, antithrombin, antiplasmin, plasminogen activator inhibitor (PAI), X-oligomers, D-dimers, prekallikrein, functional kallikrein inhibition (PKI), and fibrinectin, by chromogenic substrate and immunochemical techniques. The Proenzyme functional index (PFI) was calculated combining the results of antithrombin, plasminogen, antiplasmin, prekallikrein and fibrinectin assay.

Kallikrein was seen in all groups. The shock groups (I-II) had in addition significant decreases in platelet count, antithrombin, and plasminogen. Fibrinogen, F VIIIIC, vWF:Ag, X-oligomers, and D-dimers were significantly higher than normal in all groups. These patients had higher levels of fibrin than non-shock patients. PAI was within the normal range in survivors (I-II), but was elevated ten-fold and increased progressively over 3 days in the non-survivors. vWF:Ag showed a similar progressive increase in non-survivors; these variables were the best early indicators of non-survival. TAT was significantly lower in shock patients (II-III), but did not discern between survivors and non-survivors during days 1-3. The results indicate a marked activation of coagulation in patients with severe infection, with more severe formation and fibrinolysis in the shock groups. High vWF:Ag and PAI in non-survivors may indicate more endothelial damage, and potentially harmful fibrinolysis inhibition.

Fibrinogens New York I and IA (NY-I and NY-II) have been purified from plasma blood samples of a sister and a brother in a White family with thrombotic tendency. Both are heterozygous and carry both through thrombin labile fibrinogen with two normal a-chain and thrombin-nonlable fibrinogen with two abnormal a-chains. The abnormal a-chains result from deletions of amino acid residues 9-72, which are encoded exactly by exon II of the gene. To study the genetic disorder for this deletion, genomic DNA's were isolated respectively from leukocytes of NY-Ia, NY-Ib (a nonaffected brother), and 48 normal individuals outside the NY-I family, and analysed in Southern blotting experiments with a human genomic DNA probe containing exon 4-7. Digestion of various DNA's were performed with two different restriction endonucleases, and these digestions were examined respectively by agarose electrophoresis.

Deletion with Hind III reveals 3 cleavage sites (one site in intron A near exon 11) with formation of two fragments of equal size (2 bands: 3.1 kb and 3.1 kb) in normal, NY-Ia and NY-IIa, but an extra fragment (one and 6.0 kb) in NY-Ib. Deletion with Pst I reveals 3 cleavage sites (one site in exon II) with formation of two fragments (2 bands: 7.5 kb and 2.9 kb) in normal, NY-Ia and NY-IIa, but an extra fragment (one and 5.7 kb) in NY-Ib. These results show that one Hind III and one Pst I cleavage sites which are present in the normal allele are absent in the abnormal allele of NY-Ia. Thus, these studies indicate that a gene disorder is associated with the patient (NY-Ia) with a thrombotic tendency, and further suggest that the genetic defect in the abnormal allele is near the junction of intron A and exon II. A possible mechanism for this genetic disorder is due to that an inverse double crossover have taken place in a region covering this junction, resulting in a chromosomal recombination event.

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CONGENITALLY ABNORMAL FIBRINOGENS

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ANOMALOUS FIBRINOGEN (FIBRINOGEN MAPLES) CHARACTERIZED BY DEFECTIVE INHIBITION AND FIBRIN CLOTTING PROPERTIES WITH ARTERIAL THROMBOSIS. G. Di Minno, A.H. Cerbone, F. Carillo, M. Colucciu, N. Serrazzano, G. Di Santo, P.L. Mattioli, M. Manzini and C. Marthourott. University of Calabria at Catanzaro and Department of Internal Medicine and Metabolic Disease, II Medical School, Naples University, and Department of Clinical Pathology, Bari University, Italy.

Prolonged thrombin time (partially corrected by calcium chloride) and normal reptilase time were found in the plasma of two siblings with arterial thrombosis. Their purified fibrinogens showed similar abnormalities as well as impaired fibrinogen platelet aggregation and ATP secretion from platelets exposed to sub-threshold concentrations of ADP or epinephrine. Hirudin suppressed the enhancing effect of the supernatants and substitution of thrombin for d-thrombin led to normalization of platelet response. Studies on fibrinolysis showed that the abnormal fibrinogen from these patients as well as its naturally occurring derivative fibrin are highly resistant to lysis by plamin. Thus our data support the concept that, in addition to the enhanced activation of platelets by residual d-thrombin, thrombosis in these patients is the result of an impaired sensitivity of fibrinogen the lytic effect of plamin.