ANTITHROMBIN III

ANTITHROMBIN III AN HEREDITARY ABNORMAL ANTITHROMBIN III (AT III) WITH DEFECTIVE HEAPRIN COFACTOR ACTIVITY. Ph. de Moerloose, G. Reber, Ph. Minazio, C.A. Bouvier, Haemostasis Unit, Geneva University Hospital, Geneva, Switzerland.

A 43-year old man presented a pulmonary embolism. Despite a negative family history for thromboembolic disorders, the unusual circumstances of apparition and the relatively young age of the patient prompted us to study carefully the coagulation parameters. Routine coagulation tests, as well as plasminogen, alpha-2-antiplasmin, protein C and protein S were all within normal range. Biological and immunological assays of AT III were performed on 12 members of the family and showed a low AT III activity in the propositus and other members of this family (mean SD5), but normal immunologic levels. Crossed immunoelectrophoresis in absence of heparin showed a normal pattern, but in presence of heparin showed an abnormal peak as compared with controls. Kinetics experiments showed a normal inhibition of Xa and IIa in absence of heparin, but abnormal in presence of heparin. An affinity chromatography on heparin Sepharose revealed two populations of AT III, one of which was devoid of heparin cofactor activity.

The toponym AT III Geneva is proposed for this new familial abnormal AT III with defective heparin cofactor activity. This family confirms the low incidence of thromboembolic events reported in this type of AT III variant.

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A functional antithrombin III (AT III) deficiency has been identified in three generations of a family with a high incidence of deep venous thrombosis. The deficiency presented as a 50% reduction in its heparin cofactor activity compared to its antigen concentration. No abnormality was detected by crossed immunoelectrophoresis of plasma in the presence or absence of heparin. Plasma from the propositus was precipitated with dextran sulphate, applied to heparin-Sepharose and the AT III eluted with NaCl. The AT III had a reduced ability to inactivate thrombin, when this was monitored by substrate hydrolysis or by SDS PA gel electrophoresis. Its mobility was normal when examined by the latter technique on 10-20% gels under reducing and non-reducing conditions. Patient AT III was reapplied to heparin-Sepharose and eluted with a NaCl gradient. A minor active pool eluted in the same concentration range, 0.9-1.2M, used to purify normal AT III, while predominantly inactive AT III eluted at higher NaCl concentrations, 1.2-2.0M. Further purification of variant AT III was achieved by passage of heparin-Sepharose eluates through a thrombin-Sepharose column and structural studies are being undertaken on this material. It is concluded that AT III Glasgow has increased affinity for heparin but reduced ability to inactivate thrombin. It can be differentiated from two other AT III variants that bind heparin with high affinity, Milano and Northwick Park, but has similar features to those of AT III Chicago.

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It has been shown previously that antithrombin III Northwick Park (AT III NWP) has reduced ability to inactivate thrombin and is characterised by an additional anodal component on crossed immunoelectrophoresis. We have applied plasma from an affected family member to heparin-Sepharose and eluted the AT III with a salt gradient. Evidence will be presented that the anodal component has higher affinity for heparin than normal AT III. Furthermore, this variant component is present in plasma as a MW >120,000 inactive complex whose tryptic peptide FAB map contains numerous signals not characteristic of normal AT III. This complex can be reduced with dithiothreitol to two non identical bands on SDS PAGE with MW ~50,000, only one of which reacts with anti-AT III. Using ion-exchange chromatography and HPLC these two components have been isolated and separated. The N-terminal sequence of the protein that does not react with anti-AT III is believed to be Asp-Ala-His-Ile-Ser-Glu. Structural investigations on the variant AT III are underway.

A NEW ASYMPTOMATIC TYPE III VARIANT OF ANTITHROMBIN III WITH DECREASE HEAPRIN COFACTOR ACTIVITY: AT III ANIEMS. B. ROUSSEL, J. DIEVAL, S. GROSS, J.F. CLAISSE, J. DELOZEL. Laboratoire d’Hematologie, Centre Hospitalier Universitaire, AMIENS, FRANCE.

A qualitative abnormality of AT III suggested by the discrepancy between a normal level of AT III antigen (0.33 g/l) and a decreased heparin cofactor activity (60% of normal) was discovered in a 37 years old woman during a routine laboratory examination for oral contraceptive. The propositus was asymptomatic as she did not develop any thrombo-embolic disease during three previous pregnancies. There was no familial history of thromboembolism. The AT III level measured by radial immuno-diffusion was within the normal range. The progressive anti factor IIa and anti factor Xa activities (chromogenic substrates CBS 3 447 and CBS 3 132) were normal (92% and 100%). Plasma and serum crossed immunoelectrophoresis (CIE) showed a normal pattern. In the presence of heparin, anti factor IIa and anti factor Xa activities were decreased (60% and 45%). Plasma and serum crossed immunoelectrophoresis showed an abnormal slow moving peak exhibiting the same mobility as antithrombin III to bind completely to heparin. CIE with various other glycosaminoglycans are on experiments.

Familial study revealed that the daughter of the propositus was carrying the same molecular abnormality.

We conclude that AT III Aniens is an hereditary type III variant.