

ANTITHROMBIN III DEFICIENCY IN A LARGE FAMILY WITH 41 AFFECTED MEMBERS. J. Stibbe, S. Adhin, G.L. Ong, R.S. Panday, S.H. Peters, S.J. Smith, L.A. Snel and L.N. Went. University Hospital Dykzigt and Municipal Hospital "Bergweg", Rotterdam, Holland; State University, Leiden, Holland and Medical Scientific Institute, Paramaribo, Suriname.

Hereditary Antithrombin III (AT III) deficiency was found in a large Hindustani family, living partly in the Netherlands, partly in Suriname. Of 201 members investigated 35 were found to be affected: AT III activity (chromogenic substrate) and AT III antigen (immuno-electrophoresis according to Laurell) were about 45%. Analysis of this family clearly demonstrated the autosomal dominant inheritance of the condition. Six non-investigated members (1 living, 5 non-living) were diagnosed as being affected on the basis of affected offspring. Seventeen affected members had no signs of thrombo-embolic (TE) processes (age group 0-10 years old, n=2; 11-20, n=5; 21-30, n=4; 31-40, n=4; 41-50, n=2). Thirteen showed clinical or proven signs of TE processes (first time in age group 0-10 years old, n=0; 11-20, n=1; 21-30, n=6; 31-40, n=4; 41-50, n=1; 51-60, n=0; 61-70, n=1). No clinical information is yet available on the remaining affected members. Deep venous thrombosis (DVT) occurred in 9 patients (age group 21-30, n=5; 31-40, n=3; 61-70, n=1). Triggering factors were none 4, surgery 1, oral contraceptives and pregnancy 4. Pulmonary embolism occurred in 6 patients (2 clinical, 4 proven) and was fatal in 4; ages were 19, 21, 26, 37, 48 and 68 years old. Pregnancy was uncomplicated in 3 women (total of 4 pregnancies), one of these women was treated prophylactically with anticoagulants during pregnancy (1 pregnancy). Two women (2 pregnancies) had a thrombotic episode (1st and 3rd pregnancy respectively) and 1 woman died suddenly 7 days after her 7th childbirth. DVT occurred in 2 of 4 women who used oral contraceptive pills. In some symptomless patients (age 22, 26, 32, 33, 40 years old) impedance plethysmography (n=5), ^{125}I -fibrinogen leg-scanning (n=3), ^{125}I -fibrinogen $T_{1/2}$ (n=3) and ^{51}Cr -platelet survival (n=1) were normal.

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ISOTOPIC AND IMMUNOLOGICAL HALF-LIFE DETERMINATION OF ANTITHROMBIN III IN VARIOUS TYPES OF ANTITHROMBIN III DEFICIENCY. G. Sas, T. Kremmer, B. Spät and I. Petó. First Department of Medicine, Postgraduate Medical School, National Oncological Institute and National "F. J. C." Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary.

Using the modified crossed immunoelectrophoresis technique (Heparin in agarose), different patterns were obtained characterizing the various types of antithrombin III (AT-III) deficiency. ^{125}J labelled and purified commercial (KABI, Stockholm) AT-III prepartes were administered to patients of different types in order to determine the biological half-life of AT-III. Various methods, including crossed immunoelectrophoresis and disc electrophoresis as well as heparin-Sepharose 4B chromatography were applied for the characterization of the AT-III administered.

These techniques revealed the molecular heterogeneity of AT-III prepartes, especially those labelled by ^{125}J . In the light of these observations it became obvious that among the AT-III determinations the most reliable and most specific method is the quantitative measurement of the fast migrating AT-III component (I-AT-III₁) obtained by the modified method of crossed immunoelectrophoresis. This component corresponds to the "natural" AT-III of fresh normal plasma.

Applying this technique, one of our propositi (B. I.) displayed a significant shortening of the biological half-life of AT-III (26 hrs) while the two others (M. L. and B. J.) had approximately normal time courses (55 and 52 hrs, respectively). The different biological half-life times of AT-III in these patients also support the assumption of the heterogeneity of the congenital AT-III deficiency.

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INHERITED DEFICIENCY OF ANTITHROMBIN III IN TWO ITALIAN FAMILIES. DIFFERENT BEHAVIOUR AFTER LONG-TERM ANTICOAGULANT TREATMENT. C. Manotti, M. Pini, R. Poti and R. Quintavalla. 5th Medical Division and Centre for Haemostatic Diseases, Ospedali Riuniti, Parma, Italy.

An inherited deficiency of antithrombin III (AT III), measured with four different, functional and immunological, methods, was found in 8 out of 11 examined members and in 3 out of 11 examined members of two Italian families (D.M. and A. families). Biological activity, measured with Abildgard's clotting assay and with an amidolytic method, ranged between 17 and 75%. Cross immunoelectrophoresis, with or without heparin, performed in the two propositi and in 4 other relatives, showed a normal pattern of migration.

A different behaviour of AT III after anticoagulation with acenocoumarin was seen in two long-term treated subjects. The proposita of the D.M. family, who had a history of recurrent thrombotic accidents, did not show any increase of AT III levels, measured in the first two weeks and after 6 and 12 months of therapy. A significant (about 50%) increase both with the functional and immunological methods was on the contrary observed in the propositus of A. family, who had undergone surgery because of mesenteric vein thrombosis. Until now both patients have been free of thrombotic recurrences.

Our findings confirm previous reports of variable effects of oral anticoagulants on AT III levels in subjects with congenital deficiency.

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ANTITHROMBIN III IN CHRONIC LIVER DISEASES. K. Rak, Z. Boda, M. Misz and P. Beck. Second Department of Medicine, University Medical School Debrecen, Hungary.

One of the most constant abnormal laboratory results in chronic liver diseases is the low antithrombin III /AT-III/ activity measured in a properly sensitive system. Two functional assays have been used in our laboratory: /a/ coagulation test based on the progressive neutralization of thrombin with clotting time determinations in the presence of small amount of heparin and without it; results were expressed as plasma AT-III index or PAT-value, and /b/ amidolytic method on synthetic chromogenic substrate.

Results of the last years can be summarized as follows: /1/ the measurement of AT-III in liver diseases /more than 300 cases, mostly cirrhosis/ is of diagnostic significance: a high index, hence a low AT-III activity, particularly in a system containing heparinized plasma is much more characteristic in cases of liver cirrhosis than results of other conventional clotting tests /prothrombin time, partial thromboplastin time, plasma fibrinogen and FDP level/; /2/ the observations may have theoretical importance, furnishing additional data on the pathophysiological role of AT-III and providing the first and strong evidence for the adverse effect of heparin in thrombin-antithrombin interaction. The level of this natural anticoagulant synthesized in liver may be reduced by increased consumption accompanying disseminated intravascular coagulation. Though it is not frequent, it must be taken into consideration, first of all in active chronic hepatitis.