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PROTEIN C : ROUEN - A NEW HEREDITARY PROTEIN C ABNORMALITY WITH LOW ANTICOAGULANT BUT NORMAL AMIDOLYTIC ACTIVITIES. J.Y. Borg, M. Vasse, M. Monconduit
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During the last three years, we could detect hereditary quantitative protein C (PC) deficiency in 43 patients belonging to 18 families. In those defects type I without oral anticoagulant treatment, the values of PC measured either by an ELISA method (PC:Ag) or by a chronometric functional assay were very closed and well correlated. (Results expressed in % of normal pooled plasmas PC:Ag m=44,1 %, SD = 15,3 ; PC : activity m = 49,5, SD = 13,5 - correlation r = 0,82). In a 32 years old man with a severe thrombo-embolic disease and in 11 related people, we could diagnose a hereditary qualitative PC deficiency type II, because of a discrepancy between normal PC:Ag levels (m = 105 %, SD = 20,3, range = 78-143) and low PC anticoagulant activities (m = 46 %, SD = 9,5, range = 30-60). Functional PC studies included assays, with or without preliminary adsorption on baryum citrate or aluminium hydroxide, with various PC activators (thrombin, PROTAC® venom), in chronometric and amidolytic assays. (Normal protein S levels were first tested).

methods	"Staclot" PC diagn. STAGO	Francis	"Stachrom" PC Diagn. STAGO	Bertina	Personal assay	ELISA
adsorption	-	+	-	+	+	
activation	Protac	IIa	Protac	IIa	Protac	
measure	chrono	chrono	CBS 6525	S 2336	CBS 6525	
patients m	46	47,7	100,3	109,4	125	105
SD	9,5	11,6	18,3	15,3	7	20,3
n	11	9	10	9	3	12
controls m	98,4	90	92,2	98,6	111,7	102

As shown by those results, PC activity is normal in amidolytic assays even after preliminary adsorption whatever the activation is. On the contrary, the PC anticoagulant activity is reduced in any technique. We can conclude that the activation is normal. Crossed immunoelectrophoresis (CIE) with or without calcium showed normal migration as compared to controls. Normal adsorption on insoluble salts and normal Ca-binding in CIE allow us to say that the abnormal PC is not completely acarboxylated. As amidolytic assays (normal in patients) do not assess the ability of activated PC to interact with protein S (PS) and phospholipids via calcium, 3 hypothesis can explain the functional abnormality:

- abnormal binding to PS
- abnormal binding to phospholipids due to partially carboxylated glutamic acids (which would be sufficient to promote adsorption)
- defective inhibition of Va and VIIIa because a conformational change allowing only hydrolysis of little synthetic peptides.

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NEONATAL HOMOZYGOUS PROTEIN C DEFICIENCY. PROBLEMS IN DIAGNOSIS AND MANAGEMENT. F. Civantos (1), J. Kent (2), C.H. Pegelow (3). J. B. Miale Coag. Lab, Departments of Pathology and Pediatrics, University of Miami School of Medicine, Miami, FL, U.S.A.

A newborn with a large rapidly necrotizing hematoma in the right buttock had initial coagulation studies suggestive of disseminated intravascular clotting. Negative cultures, development of other ecchymotic lesions in the scalp, eyelid, and elbows and response to fresh frozen plasma allowed the clinical diagnosis of homozygous protein C deficiency that was confirmed by protein C levels of .00 U/ml immunological and .085 U/ml by coagulation assay. Immunologic protein C assays in the family showed: .41 U/ml in the mother, .38 U/ml in the father, and .55 U/ml in the paternal grandfather with similar functional assay values. CT scans showed thrombosis of dural venous sinuses with bilateral infarcts and possible subarachnoid hemorrhage resulting in rapidly developing hydrocephalus. Cataracts and synechiae developed in both eyes as a result of hemorrhage at birth. Further episodes of thrombosis and hemorrhage were prevented by administration of fresh frozen plasma every 12 hours. Problems ensued with development of hyperproteinemia, hypercalcemia and hyperphosphatemia. A shunt to control the hydrocephalus became infected as did the catheter for fresh frozen plasma administration. Coumadin administration concurrent with fresh frozen plasma administration was difficult to regulate; phenobarbital given for subclinical status epilepticus interfered with Coumadin. Factor VII assays were used to regulate the concomitant administration of Coumadin and fresh frozen plasma. At 8 months a new episode of purpura fulminans caused the patient's demise. Skin biopsy of the lesions at birth and autopsy sections of new skin lesions showed thrombosis of subcutaneous adipose tissue veins with surrounding hemorrhage. The pathologic and dermatologic findings were identical to those of Coumadin-induced skin necrosis.

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TWO CASES OF NEONATAL PURPURA FULMINANS HOMOZYGOUS FOR PROTEIN C DEFICIENCY IN A CHINESE FAMILY. M.C. SHEN (1), S.H. CHEN (2) AND K.S. LIN (1). Department of Clinical Pathology (1) and Department of Pediatrics (2) College of Medicine, National Taiwan University, R.O.C.

Protein C (PC) deficiency associated with hereditary venous thromboembolic disease was first reported in 1981 and is inherited as an autosomal dominant disorder. The prevalence of heterozygous PC deficiency is estimated to be 1 to 4% in venous thrombotic diseases. The homozygous PC deficiency is even rare, and has been reported in only about 10 families througout the world. It usually presents in newborn infants as purpura fulminans or severe thrombotic disease. We herein report two newborn brothers in a Chinese family, who manifested with purpura fulminans soon after birth and died at age of 21 days and 27 days respectively. Vitamin K was administered to the second baby after birth. Both parents are not consanguineous and there were no family histories of thromboembolism on paternal and maternal sides. Blood sample was not available for specific studies in the first baby. PC antigen level by electroimmunoassay was <6% in the second baby and 49% and 60% respectively in their mother and father. Antithrombin III activity by amidolytic method was 49% in the second baby, and 90% and 97% respectively in their mother and father. Vitamin K-dependent coagulation factors and factor V were within the expected range for a newborn. Factor VIII and fibrinogen level were notably decreased. Autopsy findings of the two newborns demonstrated the similar pictures characterized by fibrin thrombi in blood vessels causing extensive hemorrhagic infarts of skin, lung, liver, kidneys, testis, urinary bladder, esophagus and brain. Our Data indicate that neonatal purpura fulminans can be familial and caused by severe homozygous PC deficiency.

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ASSOCIATION OF HEREDITARY DYSFIBRINOGENEMIA WITH PROTEIN C DEFICIENCY IN TWO PATIENTS WITH THROMBOTIC TENDENCY. S. Gandrille, P. Priollet, L. Capron, M. Roncato, J.N. Fiessinger, M. Aiach. Hôpital Broussais, Paris, France.

An abnormal fibrinogen was found to be associated with protein C deficiency in two unrelated patients. Both were symptomatic, one having severe complicated atherosclerosis, the other recurrent venous thrombosis. In both cases, the two abnormalities coexisted in several members of the family. The two abnormal fibrinogens (Poitiers and Argenteuil) were purified from the patients' plasma and compared to fibrinogens purified from several normal subjects. Polymerisation was abnormal in both cases in presence of reptilase and thrombin.

The kinetic of proteolysis by plasmin was studied during 24 hours using SDS-polyacrylamide gel electrophoresis. In the first case, the appearance of fibrinogen degradation products (FDPs) was slightly delayed. The most sliking abnormalities were observed with fibrinogen Argenteuil which still contains "early" FDPs (X and Y) at 24 h while the normal fibrinogens were all completely degraded.

The stimulating effect of fibrin on plasminogen activation by tPA was studied after insolubilization of the purified fibrinogen according to the SOFIA technique described by Angles-Cano (Anal. Biochem. 1985, 153, 201). Only fibrinogen Argenteuil was found to have a decreased catalytic effect on plasmin formation.

Thrombin binding by fibrin clots, studied according to Haverkate (Thromb. Haemostas. 1986, 55, 131) was found decreased in fibrinogen Poitiers and normal in fibrinogen Argenteuil.

Conclusion: In these two cases of hereditary dysfibrinogenemia least one of the natural antithrombotic function elicited by fibrinogen-fibrin transformation was found to be strongly abnormal. Both fibrinogens presented abnormal lysis by plasmin, particularly fibrinogen Argenteuil in which fibrin degradation was also reduced. This functional abnormality have already been described in patients with thrombotic tendency. It is however difficult to conclude, as in both families the dysfibrinogenemia was associated with protein C deficiency.