Case report

Portal vein thrombosis with ruptured oesophageal varices as presenting manifestation of hereditary protein C deficiency

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SUMMARY The protein C system is essential in limiting the activation of coagulation in vivo. We report the case of a 45 year old man with portal vein thrombosis complicated by ruptured oesophageal varices. Low concentration of plasma protein C was found in the patient and subsequently in one brother with a history of venous thromboembolism, and also in one son and one nephew who were asymptomatic. Hereditary protein C deficiency should be considered in patients with portal hypertension due to portal vein thrombosis.

In up to 50% of adults with portal vein thrombosis, the cause of vascular obstruction cannot be elucidated.1-3 Protein C had recently been identified as a major factor regulating thrombin generation. Hereditary deficiency in protein C was associated with a high risk of thromboembolic disease.4-6 Manifestations include superficial thrombophlebitis, deep venous thrombosis, and/or pulmonary embolism,4,6 cerebral venous thrombosis,7,8 and mesenteric vein thrombosis.9,10 Protein C is a vitamin K-dependent zymogen of a serine protease11 and is synthesised in the liver.12 It is converted to its activated form in a reaction catalysed by a complex formed between thrombin and thrombomodulin, an endothelial cell surface protein.13,14 Activated protein C inhibits activated factors V and VIII15 and stimulates fibrinolysis through the inactivation of the tissue plasminogen activator (t-PA) inhibitor.16,17

In a prospective study of 40 consecutive adult patients with portal vein thrombosis, we have identified one patient with hereditary protein C deficiency, whose case is reported here.

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Case report

In December 1986, a 45 year old man (Figure, II-4) was admitted to Hôpital Beaujon for melaena. In 1984, he suffered from an unexplained bout of abdominal pain. In May 1986, after a first episode of melaena, endoscopy showed oesophageal varices; serum gamma glutamyl transpeptidase was three times the upper limit of normal; the patient received 2 units of packed red blood cells. There was no personal history of venous thromboembolism, but one older brother (Figure II-2) had suffered from deep venous thrombosis of the leg complicated by pulmonary embolism and from myocardial infarction at ages 55 and 56, respectively.

On admission, clinical examination was normal. Laboratory tests gave the following results: erythrocyte count 4-87 10⁹/l, haemoglobin 15-1 g/dl, leucocyte count 6-8 10⁹/l, platelet count 154 10⁹/l; ALT 35 IU/l (N<40 IU), serum alkaline phosphatase 101 IU/l (N<130 IU), serum albumin 4-0 g/dl, serum globulin 1-2 g/dl; prothrombin time was found in the normal range. Fibroscopy showed large oesophageal varices and no other lesion. Ultrasound examination disclosed atrophic right liver lobe,
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Figure  Pedigree of the proband (II-4) presenting with portal cavernoma: heterozygote for protein C deficiency. X=investigated.

patent hepatic veins, obliterated right portal vein but patent left portal vein. The portal vein could not be identified in the porta hepatis which was occupied by several abnormal tubular structures suggestive of cavernous transformation. Abdominal computed tomography scan confirmed the presence of a portal cavernoma. The gradient between wedged and free hepatic venous pressure was 2 mmHg (normal, 2–4 mmHg). Histologic examination of a liver specimen showed no abnormality.

Search for a myeloproliferative disease using determination of total red cell mass, bone marrow biopsy and cultures of bone marrow cell\(^a\) was negative. There was no laboratory evidence of paroxysmal nocturnal haemoglobinuria or lupus anticoagulant. As shown in the Table, a type I protein C deficiency was found,\(^b\) as functional\(^c\) and immunoenzymatic\(^d\) assays gave low values for plasma protein C. There was no deficiency in protein S,\(^e\) antithrombin III,\(^f\) plasminogen,\(^g\) or heparin cofactor II.\(^h\)

During the hospital stay, the patient developed thrombosis of the left superficial femoral vein. He was treated with intravenous sodium heparin and, subsequently, with warfarin and coumarin.

A study of the patient’s family showed deficiency in protein C in the brother of the proband (Figure, II-2), in one asymptomatic son aged 24 (Figure, III-4), and in one asymptomatic nephew aged 32 (Fig. III-1). Proband’s father died at age 69 from silicosis. Proband’s mother, aged 85, was alive with varicose veins and trophic cutaneous ulcers of the legs; she could not be tested for protein C.

Discussion

Deficiency in protein C can be inherited and is then most often transmitted as an autosomal dominant trait with various penetrance.\(^b\)\(^c\)\(^d\)\(^h\)\(^i\)\(^j\)\(^k\) A low level of plasma protein C can also be acquired as a result of disseminated intravascular coagulation,\(^k\) which was not present in any of the affected members of this family. More commonly, deficiency in protein C is the consequence of liver disease and is then associated with decreased level of other coagulation factors. Impairment of liver function which can result from portal vein thrombosis,\(^i\) cannot account for the low protein C level in our patients, as the levels of other coagulation factors were normal. In this family, protein C deficiency was found in two asymptomatic young men, in one patient with a typical history of thromboembolism, and in the proband with portal cavernoma, a likely sequella of earlier thrombosis (Figure). Thus, protein C deficiency detected in the propositus is compatible with a defect inherited as an autosomal dominant trait.

It is not clear whether the unexplained bout of abdominal pain which occurred two years before corresponded to the constitution of thrombosis, to a resolutive episode of intestinal ischaemia secondary to mesenteric vein thrombosis, or to an unrelated illness. There are other cases of deficiency in protein C, protein S, or antithrombin III, manifested by mesenteric vein thrombosis.\(^h\)\(^i\)\(^j\)\(^k\) In these latter cases, the manifestations were those of acute intestinal ischaemia or infarction. Among our 40 patients with portal vein thrombosis prospectively tested for protein C, this is the first case of chronic portal hypertension caused by hereditary protein C deficiency and we are not aware of any similar reported case. Only one case of portal hypertension consecutive to portal vein thrombosis and related to an inherited protein S deficiency has already been reported; the patient was a young girl suffering from recurrent variceal bleeding from age 10.\(^h\)
Our estimate of the prevalence of inherited protein C deficiency in portal vein thrombosis (2%) is higher than the figures reported for thrombosis of unselected site.\(^9\)\(^{2}\) We propose that levels of protein C, as well as protein S and antithrombin III, be measured in patients with portal vein thrombosis, when no overt cause is present.

Prevention of recurrent thrombosis by coumarin derivatives is mandatory in patients with hereditary deficiency in protein C. Management of patients with previous variceal bleeding appears particularly difficult, however. Portosystemic shunting is usually not feasible in patients with portal vein thrombosis.\(^1\)\(^{2}\) In the present case, we reasoned that propranolol may prevent recurrent varical bleeding.\(^3\) Endoscopic sclerotherapy may also be considered. The risk of bleeding from oesophageal ulcers after sclerotherapy\(^4\) might be increased by anticoagulation. This concern led to the use of propranolol as a first line method.

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References

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