Acute Budd-Chiari syndrome with hepatic failure and obstruction of the inferior vena cava as presenting manifestations of hereditary protein C deficiency

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Abstract
The protein C system is essential in limiting the activation of coagulation in vivo. We report on a 29 year old woman with Budd-Chiari syndrome and occlusion of the inferior vena cava who presented with acute liver failure. She was successfully treated with an emergency mesoatrial shunt. Eight months after surgery, she has no ascites and normal liver function. She had a low concentration of plasma protein C on admission to hospital and during the follow up. Protein C deficiency subsequently was found in her father and two sisters, who were asymptomatic. Hereditary protein C deficiency should be considered in patients with Budd-Chiari syndrome.

Budd-Chiari syndrome is a rare disorder whose cause remains unknown in one third of patients. This syndrome has, however, been associated with a variety of conditions including malignancy, treatment for malignancy, polycythaemia rubra vera, paroxysmal nocturnal haemoglobinuria, other primary myeloproliferative disorders, pregnancy, hepatic amebiosis, oral contraceptives, and less usual causes such as ingestion of pyrrolizidine alkaloid-containing teas, aspergillus infections, hydatid cysts, antithrombin III deficiency, and Behçet disease.

Protein C is a major factor regulating thrombin generation. Hereditary deficiency in protein C is associated with a high risk of thrombotic disease. Manifestations include superficial thrombophlebitis, deep venous thrombosis or pulmonary embolism, or both; cerebral venous thrombosis, and splanchic venous thrombosis.

Protein C is a vitamin K-dependent zymogen of a serine protease and is synthesised in the liver. It is converted to its activated form in a reaction catalysed by a complex formed between thrombin and thrombomodulin, an endothelial cell surface protein. Activated protein C inhibits activated factors V and VIII and stimulates fibrinolysis through the inactivation of the tissue plasminogen activator (t-PA) inhibitor.

We present the first case of acute hepatic vein thrombosis in a patient with a history of oral contraceptive usage and recent recurrent orogenital ulcers associated with hereditary protein C deficiency.

Case report
On 17 November 1988, a 29 year old Algerian woman was admitted to our liver unit with acute liver failure and ascites. There was no familial or personal history of venous thrombosis despite three previous surgical procedures, and three years earlier. In 1985 she had a normal labour and delivery. She had taken oral contraceptives from 1979 to 1984 without any problems and for three months before admission to hospital. From April 1988, the patient reported a history of recurrent orogenital ulcers.

On 2 November 1988, the patient began to suffer abdominal pain and general fatigue. Eight days later she presented to her physician with painful hepatomegaly, ascites, and bilateral leg oedema. Laboratory data disclosed an alanine aminotransferase activity of 150 IU (normal less than 33 IU), and a prothrombin time ratio of 58%.

On admission to hospital eight days later, clinical examination showed painful hepatomegaly, ascites, and bilateral leg oedema. There was no encephalopathy. Laboratory tests gave the following results: erythrocyte count 4.65 × 10¹²/l, haemoglobin concentration 13.5 g/dl, leucocyte count 13.8 × 10⁹/l with normal differential, platelet count 218 × 10⁹/l, alanine aminotransferase 992 IU/l, serum total bilirubin 32 μmol/l, serum alkaline phosphatase 187 IU/l (normal less than 230 IU), serum albumin 2.9 g/dl, serum globulin 1.3 g/dl, prothrombin time ratio 28%, and factor V 20%. Serological tests for hepatitis virus A and B, Epstein-Barr virus, and cytomegalovirus were negative. Ultrasound examination showed ascites, occluded hepatic veins, and patent portal vein. The caudate lobe was not enlarged and the inferior vena cava could not be identified, suggesting an occlusion.
Abdominal computed tomogram confirmed the hepatic venous obstruction and showed an enlarged liver with heterogeneous uptake (Fig 1). A right transfemoral venacavogram confirmed the total obstruction of the inferior vena cava at and under its intrahepatic portion.

On 18 November 1988, the patient underwent emergency surgery because of a rapid increase in the serum transaminase activities and growing deterioration of liver function. Some 21 of ascites were drained. The liver was massively enlarged and congested, with ‘dark’ patches. The portal vein pressure was 39 cm H₂O and the superior vena cava pressure was 3 cm H₂O. A mesoatrial shunt was created using a polytetrafluoroethylene (PTFE Gore-tex) reinforced prosthesis 14 mm in diameter. The graft extended from the superior mesenteric vein through the transverse mesocolon and then posteriorly to the stomach and anteriorly to the liver. A right anterolateral thoracotomy was made, the graft was placed across the anterior mediastinum, and then an end to side anastomosis was created into the right atrial appendage. Once the graft was in position and the blood flow was established, the portal vein pressure fell to 13 cm H₂O and the liver reduced in size.

The patient’s postoperative course was uneventful except for a right pleural effusion that persisted for one week. Ascites did not recur and all liver function tests were normal two weeks after surgery. Postoperative abdominal computed tomography showed a patent shunt and a normal liver (Fig 2). The patient was treated with intravenous sodium heparin and subsequently with coumarin.

In February 1989, the patient was readmitted because of fever and recurrent orogenital ulcers. Clinical examination was normal. There was no skin involvement, no cutaneous hyperreactivity, no arthritis, gastrointestinal, or ocular manifestation of Behçet syndrome. Ultrasound examination and abdominal computed tomogram failed to detect any new vascular lesion and the shunt remained patent.

Laboratory data were normal. We were unable to find any major or minor signs of Behçet syndrome other than orogenital ulcers and deep venous thrombosis.

Eight months after surgery the patient is well and Doppler ultrasound confirms the patency of the mesoatrial shunt.

During her stay in hospital, before and after surgery the search for a myeloproliferative disease was negative, but culture of bone marrow cells was not undertaken. 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, as functional and immuno-enzymatic assays gave low values for plasma protein C. There was no deficiency in protein S, antithrombin III, plasminogen, or heparin cofactor II, and the fibrinolytic tests were normal.

A study of the patient’s family (Fig 3), showed deficiency in protein C in the father of the proband (I–2) and two out of her three sisters (II–2 and II–4). All were asymptomatic except one sister (II–2), who had varicose veins.

### Discussion

Protein C deficiency can be inherited and is then most often transmitted as an autosomal dominant trait with various penetrance. A low protein C value can also be acquired as a result of disseminated intravascular coagulation, which was not present in any of the affected members of this family and was present in our patient only at the time of her first hospital admission and not later. Protein C deficiency is more commonly the consequence of liver disease, when it is associated with decreased values of other coagulation factors. Impairment of liver function, which results from Budd-Chiari syndrome, could account for the low protein C value in our patient at hospital admission, but not three months after surgery (Table) as her liver function tests and the values of other coagulation factors were normal then. In this family, protein C deficiency was found in two asymptomatic young women, in one asymptomatic man, and in the proband. Thus protein C deficiency detected in the proband is compatible with a defect inherited as an autosomal dominant trait.

Heterozygous protein C deficiency is an important independant risk factor for the development of thrombosis. However, a recent study by Mileitich et al., noted that the frequency of heterozygous protein C deficiency may be as high as 1/200 in a healthy adult population, and that biochemically affected people do not suffer a thrombotic manifestation. This study also indicates that other factors, as yet undefined, may play an important role in the clinical expression of this disorder. It is not clear whether protein C deficiency was the only cause of vascular obstruction in our patient. She took oral contraceptives for three months before the initial manifestation and these could have increased the risk of venous thrombosis by adding their thrombogenic effect.

### Results of coagulation studies in the proband and three affected members of her family

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<tr>
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<th>Normal range (%)</th>
<th>Proband (I–1) (%)</th>
<th>Family (%)</th>
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<tbody>
<tr>
<td>Factor II</td>
<td>70–120</td>
<td>46</td>
<td>70</td>
</tr>
<tr>
<td>Factor VII + X</td>
<td>70–120</td>
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<td>Factor V</td>
<td>70–120</td>
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<td>Protein C antigen</td>
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<td>70</td>
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<tr>
<td>Plasminogen activity</td>
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<td>Heparin cofactor II activity</td>
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<tr>
<td>Fibrinogen (g/l)</td>
<td>2–4</td>
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<td>3–10</td>
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to that of protein C deficiency. Moreover, the recent recurrent oesophageal ulcers and the inferior vena cava obstruction suffered by our patient may well have been underlying conditions of a 'latent' Behçet syndrome, in which a thrombogenic effect is well known. Protein C deficiency may not therefore have been the only thrombogenic condition in our patient. The estimated prevalence of protein C deficiency in portal vein thrombosis is 2%, higher than the figure reported for thrombosis of unselected sites. We suggest that values of protein C as well those of protein S and antithrombin III should be measured in patients with splanchic venous thrombosis, even when another cause is present.

Prevention of recurrent thrombosis by coumarin derivatives is mandatory in patients with hereditary protein C deficiency. Conventional medical management of acute Budd-Chiari syndrome is often unsuccessful. Mesoatrial shunt is the treatment of choice for acute Budd-Chiari syndrome in which there is complete obstruction of the inferior vena cava, despite a conflicting long term prognosis. Orthotopic liver transplantation with adjunctive anticoagulant medication may also be considered as an alternative treatment choice, particularly in patients with metabolic liver disorders such as protein C deficiency and when the course of the disease shows chronic hepatic failure. The obstruction of the inferior vena cava and the recent and rapid onset of the disease led us to use a mesoatrial shunt as a first line method. Further studies will help to determine the best procedure to be followed.

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