

fructose related gastrointestinal symptoms we prefer to take a careful dietary history, particularly of fructose-containing foods and to perform a two week trial of appropriate dietary measures, rather than performing fructose breath hydrogen tests.

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1 Kneepkens CMF, Vonk RJ, Fernandes J. Incomplete

- intestinal absorption of fructose. *Arch Dis Child* 1984;59:735-8.
- 2 Wales JKH, Primhak RA, Rattenbury J, Taylor CJ. Isolated fructose malabsorption. *Arch Dis Child* 1990;65:227-9.
- 3 Perman JA. Breath analysis. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric gastrointestinal disease*. Philadelphia: B C Decker Inc, 1991: 1354-62.
- 4 Fujisawa T, Riby J, Kretchmer N. Intestinal absorption of fructose in the rat. *Gastroenterology* 1991;101:360-7.
- 5 Barnes G, McKellar W, Lawrance S. Detection of fructose malabsorption by breath hydrogen test in a child with diarrhea. *J Pediatr* 1983;103:575-7.
- 6 Kneepkens CMF, Douwes AC, Jakobs C. Apple juice, fructose, and chronic nonspecific diarrhoea. *Eur J Pediatr* 1989;148:571-3.

Transient protein S deficiency with deep venous thrombosis during *Salmonella typhimurium* infection

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Abstract

A patient with deep venous thrombosis and low protein S activity during the course of *Salmonella typhimurium* infection is presented. Although protein S deficiency has been reported in patients with disseminated intravascular coagulation, it was not present in this patient and his protein S activity was normal after the findings of infection and deep venous thrombosis disappeared.

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Congenital protein S deficiency is inherited as an autosomal dominant trait and it may cause recurrent thrombotic disease with or without a precipitating condition.¹ Acquired decreases in protein S have been reported in pregnancy and during oral contraceptive hormone treatment and in patients with disseminated intravascular coagulation (DIC) and liver disease.² Although patients with sepsis frequently suffer thromboembolic complications,³ protein S deficiency or inactivity in these patients is often not recognised if they do not have DIC.

Here, we describe a patient who presented with deep venous thrombosis together with low protein S activity during the course of *Salmonella typhimurium* infection. He did not have any clinical and laboratory findings of DIC and his protein S activity returned to normal after the findings of infection and deep venous thrombosis disappeared.

Case report

A 13 year old boy was admitted with complaints of fever, swelling of the ankles and knees, a rash on the trunk and extremities, pain in the lumbar region, and progressive oedema. There was no history of bleeding or thromboembolic abnormalities in the patient nor in either maternal or paternal family members. Physical examination revealed fever (39.7°C), an

erythematous macular rash on the lower extremities, hepatomegaly, and pitting oedema in both pretibial regions and the dorsa of the feet.

Initial laboratory findings were: haemoglobin concentration 100 g/l, packed cell volume 0.32, white cell count $6 \times 10^9/l$, platelet count $480 \times 10^9/l$, prothrombin time 12 seconds, partial thromboplastin time 42 seconds, fibrinogen concentration 2.9 g/l, fibrinogen degradation products 10-40 µg/ml, and the Ham test was normal. Stool and blood cultures revealed *S typhimurium*. Venography of the lower extremities showed deep venous thrombosis and computed tomography showed occlusion of inferior vena cava and both iliac and femoral veins. Abdominal ultrasonography showed hepatosplenomegaly and occlusion of the inferior vena cava.

The patient was given anticoagulants with 50 U/kg/hour heparin until changed to 225 mg/day dipyridamole, and 1 g/day salicylate on day 7. For salmonella infection ciprofloxacin was started and by day 3 his temperature was normal and on day 10 oedema of the lower extremities disappeared.

On day 20, antibacterial treatment was discontinued and the patient was discharged on antiplatelet drugs. Sixty days later abdominal ultrasonography and computed tomography showed no thrombosis and the antiplatelet treatment was stopped.

Methods

Routine coagulation tests (prothrombin time, partial thromboplastin time, fibrinogen concentration) were performed in fresh plasma and fibrinogen degradation products were measured in serum using standard methods. Venous blood was drawn by direct venepuncture into Vacutainer glass tubes containing 1 part 0.13 mol trisodium citrate for 9 parts of blood, and centrifuged at 3000 rpm for 10 minutes. Plasma was then separated and stored in 0.5 ml aliquots

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Protein S activity of the patient and his family members

Family member	Age (years)	Protein S activity (%) [*]
Father	48	109
Mother	45	96
Sister 1	21	84
Sister 2	18	84
Brother	15	100
Patient:	13	
during infection		37
After infection		91

^{*}Normal value: 65–140%.

at -40°C until use. All tests were made within five days of blood collection.

Antithrombin III antigen concentration was evaluated according to a immunochemical turbidimetric method in fresh plasma using antiserum supplied by Behringwerke. Protein C activity was determined in stored plasma by the snake venom activated partial thromboplastin time assay and protein S activity by the factor Va activated partial thromboplastin time assay (in both cases using commercially available reagents from Diagnostica Stago).

Standards and test samples were run in duplicate in both protein C and protein S assays. The results of protein C and protein S activities were expressed in percent of normal plasma activity (activity in 1 ml of pooled plasma = 100% activity).

Results

During hospitalisation of the patient when *S typhimurium* infection was present, the antithrombin III antigen concentration was 40.2 mg/100 ml (normal range 0.22–0.41 mg/100 ml) and protein C activity was 71% of normal (normal range 70–140%). Protein S activity was very low at 37% of normal (normal range 65–140%). Sixty days after discharge, protein C activity remained within normal limits (84%) and protein S activity returned to normal (91%).

To exclude familial occurrence of protein S deficiency, protein S activity was studied in the patient's family. It was normal in all family members (table).

Discussion

The findings in our patient are not consistent with those reported for hereditary protein S deficiency in the literature⁴; he had no previous history of thromboembolism and none of the family members had evidence of a thrombotic

event. However, it is not possible to diagnose or exclude hereditary protein S deficiency only on the basis of the clinical features as they are not pathognomonic. Patients with heterozygous deficiency of protein S usually show their first thrombotic event in early adulthood¹ and this might have been the first thrombotic attack of hereditary protein S deficiency for our patient. Thus, the clinical findings had to be confirmed by laboratory studies. Laboratory findings consistent with the diagnosis of hereditary protein S deficiency demonstrate reduced plasma protein S antigen and/or activity in the patient and in his/her family members.⁴ Because protein S activity was normal in the patient after recovery from salmonella infection and in the family members, he must have had an acquired rather than a hereditary protein S deficiency.

Acquired decrease in protein S activity has been reported in some diseases. Our patient had *S typhimurium* infection when he developed a venous thrombosis and low protein S activity. Because septicaemia is a well recognised cause of disseminated intravascular thrombosis, Hesselvik *et al* studied protein S concentrations in the patients with severe infection and septic shock and found no deficiency.³ Madden *et al* reported two patients with purpura fulminans, a complication of DIC.⁵ Both cases had a decreased protein S concentration and one of them had oedema of the leg as in our patient, and, in contrast to those cases who had purpuric lesions, high prothrombin time, partial thromboplastin time, and concentrations of fibrinogen degradation products, our patient had no evidence of DIC.

Although chronic coumarin treatment has been effective in patients with familial protein C and protein S deficiencies and recurrent thrombosis,⁶ our patient did not need chronic anti-coagulant treatment.

- 1 Comp PC, Esmon CT. Recurrent venous thromboembolism in patients with a partial deficiency of protein S. *N Engl J Med* 1984;**311**:1525–8.
- 2 D'Angelo A, Vigano-D'Angelo S, Esmon CT, Comp PC. Acquired deficiencies of protein S activity during oral anti-coagulation, in liver disease, and in disseminated intravascular coagulation. *J Clin Invest* 1988;**81**:1445–54.
- 3 Hesselvik JF, Malm J, Dahlback B, Blomback M. Protein C, protein S and C4b-binding protein in severe infection and septic shock. *Thromb Haemostas* 1991;**65**:126–9.
- 4 Engesser L, Broekmans AW, Briet E, Brommer EJP, Bertina RM. Hereditary protein S deficiency: clinical manifestations. *Ann Intern Med* 1987;**106**:677–82.
- 5 Madden RM, Gill JC, Marlar RA. Protein C and protein S levels in two patients with acquired purpura fulminans. *Br J Haematol* 1990;**75**:112–7.
- 6 Schafer AI. The hypercoagulable states. *Ann Intern Med* 1985;**102**:814–28.