Protein C deficiency in a black South African family

A case report

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Summary

Protein C is a vitamin K-dependent anticoagulant that functions by inhibiting the activity of factors Va and VIIIa. An inherited deficiency of this protein may enhance the risk of thrombosis. The first kindred with levels of protein C that averaged 50% of normal in association with recurrent thrombotic events was described in 1981. A black South African family with an inherited deficiency of this protein is reported.

Protein C is a vitamin K-dependent protein known to function as an anticoagulant by destroying the biological activity of factor Va and VIIIa and promoting fibrinolysis and clot lysis. Low levels of thrombin can activate protein C in vivo by binding to an endothelial cell co-factor, thrombomodulin. Activated protein C is then released from the endothelial cell surface and binds to protein S, another vitamin K-dependent factor. The activated protein C-protein S complex then exerts its inhibitory effect on factors Va and VIIIa. In this manner it is able to prevent the conversion of factor X to factor Xa by factor IXa. It is clear that this inhibitory process would limit the generation of factor Xa and thereby prevent the production of thrombin. These data led to the hypothesis that an inherited deficiency of this protein might enhance the risk of thrombosis. The first case of an association of a hereditary protein C deficiency and recurrent thrombosis was described by Griffin et al. and more families were described by Bertina et al. and Pabinger-Fasching et al. At the same time, Branson et al. reported an infant with purpura fulminans neonatalis caused by an almost total lack of protein C. The disease is characterised by severe skin ecchymoses, which progress to necrosis. This is consistent with the homozygous condition of protein C deficiency. A black South African family with protein C deficiency is reported.

Case report

A 29-year-old black woman presented to Baragwanath Hospital with a history of purulent vaginal discharge, lower abdominal pain and dysuria. On examination she was found to have an acute abdomen and was subjected to laparotomy. Twenty-five centimetres of necrotic small bowel were resected with end-to-end anastomosis. Postoperatively, she developed a high-output enterocutaneous fistula but refused further surgery. The fistula closed with conservative management.

On admission to hospital this patient was also noted to have extensive bilateral venous thrombosis extending proximally to involve both iliac veins; this was confirmed by isotope venography. In the absence of an obvious underlying predisposition to venous thrombosis, she was investigated for a coagulation disorder. The investigations comprised measurement of prothrombin ratio, partial thromboplastin time, platelet count, fibrinogen level, protein C and antithrombin III levels. Tests for antinuclear factor and lupus anticoagulant completed the thrombosis profile. All these results were in the normal ranges except for a protein C level of 10% (normal 70 - 140%).

After initial management with intravenous heparin, the patient was placed on warfarin therapy with gradual resolution of the clinical sequelae.

Eight months later the patient was readmitted to hospital in a moribund and shocked state with small intestinal obstruction secondary to peritoneal adhesions. At laparotomy she was found to have diffuse gangrene involving small bowel and omentum with extensive adhesive peritonitis. Jejunostomy was performed for a jejunal fistula. In spite of an initial improvement, the patient became progressively more jaundiced over the next 4 weeks and died of hepatorenal failure.

Laboratory investigations

Venous blood was collected in 1/10 volume of 3.8% sodium citrate. Platelet-poor plasma was obtained by centrifugation of citrated blood at 2,000 g at room temperature for 20 minutes. Functional protein C was assayed using a commercially available kit. All other coagulation tests were measured using conventional techniques. The lupus inhibitor was detected by its ability to prolong the prothrombin time using 1/10 000 dilution of human brain thromboplastin. At the time of laboratory investigations, none of the patient's family were on anticoagulation therapy.

All coagulation results (except protein C) of the index case and those members of her family who could be traced were normal (Table I). Of particular note was the high fibrinogen level (9.2 g/l). The protein C results are shown in Fig. 1.

Discussion

The data presented here confirm that an isolated protein C deficiency is associated with a high risk of venous thrombosis and that it is an inherited disorder. Because both the father and the mother of the index case were dead, we were unable to establish the inheritance pattern. However, it is highly unlikely that the occurrence of 7 such patients in one family is merely accidental. The pattern of inheritance seems to be consistent with autosomal dominant transmission. This is in agreement with observations in other families.
more common types of hereditary protein C deficiency. 

In the future a more extensive analysis of a large number of patients with protein C deficiency will be needed to establish the associated risk for thrombo-embolic disease and to develop a possible strategy for treatment. To our knowledge this is the first description of a black South African family with protein C deficiency, indicating that the deficiency is not restricted to whites.

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Fig. 1. Pedigree of family with protein C deficiency.

The elucidation of the protein C system provides new tools with which to approach the problem of hypercoagulability. Although clotting tests have proved to be very useful in predicting a tendency to bleed, they have provided little help in predicting clotting disease, nor has family member aged 28 years, who has a level of 36%. This is consistent with the findings of Pabinger-Fasching et al. 11 Of interest in the index case was the very high fibrinogen level. However, this was probably due to the short-lived increase in fibrinogen that occurs with tissue injury, burns or infection.

### TABLE I. LABORATORY INVESTIGATIONS OF PROTEIN C DEFICIENT FAMILY

<table>
<thead>
<tr>
<th>Family members</th>
<th>Sex</th>
<th>Present age (yrs)</th>
<th>Protein C functional</th>
<th>PI ratio</th>
<th>PTT ratio</th>
<th>Fibrinogen (g/l)</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>K1</td>
<td>F</td>
<td>30</td>
<td>10</td>
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<td>1.24</td>
<td>9.2</td>
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DVT = deep vein thrombosis.

**REFERENCES**