**Originals**

**Protein C and S deficiency in severe infectious purpura of children: a collaborative study of 40 cases**

F. Leclerc, J. Hazelzet, B. Jude, W. Hofhuis, V. Hue, A. Martinot and E. Van der Voort

Department of Pediatric Intensive Care and the Department of Hematology, Hôpital Calmette, Lille, France and Sophia Children’s Hospital, Rotterdam, The Netherlands

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**Abstract.** We studied, in 40 children (mean age: 52 months) with severe infectious purpura, the relationships between protein C (PC) and protein S (PS) levels, and shock, disseminated intravascular coagulation (DIC) and outcome. We determined, on admission, PC antigen (ELISA) and activity (chromogenic test), and total PS (ELISA). Results were expressed as % of normal adult values. Statistical analysis was performed with SAS. Thirty children were in shock, 20 had DIC. All children with DIC, and 10 without DIC were in shock. Of 20 children who were in shock and had DIC, 3 died and 1 had an amputation. PC antigen was significantly decreased in shock children (p < 0.05), in children with DIC (p < 0.0005), and in non-survivors (p < 0.05). PC activity was significantly decreased in shock children (p < 0.05), in children with DIC (p < 0.0005), and in non-survivors (p < 0.05). Total PS was not decreased in shock children, but was significantly decreased in children with DIC (p < 0.005), and in non-survivors (p < 0.005). We conclude that PC and PS levels were decreased in our children, and that PC levels were significantly decreased in the presence of shock, DIC, and fatal outcome. PC and antithrombin III (AT III) supplementation, should be evaluated in children with severe infectious purpura with shock and DIC.

**Key words:** Infectious purpura — Purpura fulminans — Disseminated intravascular coagulation — Protein C — Protein S

Protein C (PC) and protein S (PS) are vitamin K dependent plasma proteins synthesized in the liver. In vitro studies have shown that, when PC is cleaved by thrombin in the presence of thrombomodulin, the activated PC thus formed is a potent anticoagulant and promotes fibrinolysis; PS serves as the cofactor for activated PC anticoagulant and fibrinolytic activities [1]. Microvascular thrombosis and skin necrosis with disseminated intravascular coagulation occur in severe infectious purpura [2, 3] in which PC and PS deficiencies have been reported [4–7], and in homozygous PC deficiency [8] and homozygous PS deficiency [9].

The aim of this study was to examine, in severe infectious purpura of children, the relationships between PC and PS levels determined on admission, and shock, DIC, and outcome.

**Methods**

Forty consecutive children, hospitalized with severe infectious purpura in Rotterdam (n = 22) and Lille (n = 18) between January 1988 and February 1990, were prospectively studied. Mean age was 52 months (ranging from 6–185 months). Purpura on admission was petechial in 12, ecchymotic in 20, and necrotic in 9. Neisseria meningitidis was recovered from 29 children and Hemophilus influenzae from one. No organism was identified in the remaining children, but in these cases antibiotics were started before admission.

Shock was defined [3] by two of the following criteria: systolic blood pressure less than 2 standard deviations of normal [10], capillary refill time longer than 3 s, and urine output less than 1 ml/kg/h.

The hemostatic studies, on admission, consisted of platelets, fibrinogen, factors II, V, VII, X, fibrin degradation products, and fibrin monomer measurements. We also determined on admission, antithrombin III (AT III) activity and PC activity by chromogenic test (Stago-France), PC antigen and total PS by ELISA (Stago-France); in 16 children from Lille, free PS was determined by ELISA (Stago-France). Results were expressed as % of normal adult values. DIC was defined by the combination of 3 of the following features: platelet count less than 150×10^9/l, fibrinogen less than 2 g/l, factor V less than 60%, and presence of fibrinogen degradation products or fibrin monomers.

Statistical analysis was performed using Wilcoxon rank-sum test, and analysis of covariance for age-adjusted comparisons, with a general linear model procedure (Statistical Analysis System, Cary, NC).

**Results**

Mean age, frequency of shock and DIC, between children from Rotterdam and those from Lille were not statistically different. Mean age between shock and nonshock chil-
Table 1. Hemostatic variables (mean ± SD) on admission in 40 children with severe infectious purpura

<table>
<thead>
<tr>
<th>Variable</th>
<th>Shock + (n = 30)</th>
<th>Shock - (n = 10)</th>
<th>DIC + (n = 20)</th>
<th>DIC - (n = 20)</th>
<th>Non-survivors (n = 7)</th>
<th>Survivors (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (10^9/l)</td>
<td>103 ± 14 **</td>
<td>217 ± 29</td>
<td>60 ± 37 ***</td>
<td>203 ± 81</td>
<td>44 ± 18 **</td>
<td>150 ± 95</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.8 ± 2.7 **</td>
<td>5 ± 1.4</td>
<td>1.3 ± 1 ***</td>
<td>5.4 ± 2.1</td>
<td>0.3 ± 0.4 ***</td>
<td>4 ± 2.4</td>
</tr>
<tr>
<td>Factor II (%)</td>
<td>50 ± 27 *</td>
<td>66 ± 13</td>
<td>36 ± 18 ***</td>
<td>72 ± 16</td>
<td>25 ± 18 **</td>
<td>60 ± 22</td>
</tr>
<tr>
<td>Factor V (%)</td>
<td>44 ± 39 *</td>
<td>74 ± 30</td>
<td>21 ± 14 ***</td>
<td>80 ± 32</td>
<td>11 ± 7 **</td>
<td>60 ± 37</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>25 ± 20 NS</td>
<td>32 ± 17</td>
<td>19 ± 11 NS</td>
<td>33 ± 22</td>
<td>20 ± 14 NS</td>
<td>28 ± 20</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>58 ± 39 NS</td>
<td>56 ± 25</td>
<td>41 ± 18 **</td>
<td>73 ± 41</td>
<td>32 ± 20 NS</td>
<td>63 ± 35</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; +, present; -, absent
NS, not significant; *p<0.05; **p<0.005; ***p<0.0001

Discussion

On admission of our patients, PC deficiency was always present, even in the absence of shock and DIC; PC defi-