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

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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, 7 died and 3 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 < 0.005). 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 150x10⁹/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

Fig. 1. Protein C antigen levels on admission (mean±SD) expressed as % of normal adult values in severe infectious purpura. DIC, disseminated intravascular coagulation; +, present; -, absent

Fig. 2. Protein C activity levels on admission (mean±SD) expressed as % of normal adult values in severe infectious purpura. DIC, disseminated intravascular coagulation; +, present; -, absent

Fig. 3. Total protein S levels on admission (mean±SD) expressed as % of normal adult values in severe infectious purpura. DIC, disseminated intravascular coagulation; +, present; -, absent

Discussion

On admission of our patients, PC deficiency was always present, even in the absence of shock and DIC; PC deficiency, between children with and without DIC, and between survivors and non-survivors, were not statistically different.

Of the 30 children 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, 7 died (2 from Rotterdam and 5 from Lille: difference not significant) and 3 survived with amputation; no child without shock or DIC died.

Common hemostatic variables are shown in Table 1. In our children as a whole, factor II levels correlated with PC antigen, PC activity, and total PS levels (p<0.005); factor VII levels correlated with PC activity levels (p<0.05), but did not correlate with PC antigen, and total PS levels; factor X levels correlated with PC antigen, PC activity, and total PS level (p<0.05). PC antigen, PC activity and total PS levels in the different groups of children are shown in Figs. 1–3. PC antigen and PC activity were significantly decreased in shock children, in children with DIC, and in non-survivors. Age-adjusted levels of PC antigen and PC activity were also significantly decreased in shock children, in children with DIC, and in non-survivors (PC antigen: shock children/non-shock children (p<0.05), children with DIC/children without DIC (p<0.0005), non-survivors/survivors (p<0.05); PC activity: shock children/non-shock children (p<0.05), children with DIC/children without DIC (p<0.0005), non-survivors/survivors (p<0.0005). Total PS was not different between shock and non-shock children but was significantly decreased in children with DIC and in non-survivors. Age-adjusted levels of total PS were also significantly decreased in children with DIC (p<0.005), and in non-survivors (p<0.005). In the 16 children in whom free PS levels were determined, free PS level (mean±SD = 36±15) correlated (p<0.005) with total PS levels (mean±SD = 39±18); because of the small number of free PS level determinations, comparisons between the different groups were not performed. AT III activity was also significantly decreased in shock children (shock children: 55±21/non-shock children: 73±19; p<0.05), in children with DIC (children with DIC: 47±16/children without DIC: 72±20; p<0.0005), and in non-survivors (non-survivors: 42±22/survivors: 63±20; p<0.05).