PROTEIN S ANTIBODIES IN ACQUIRED PROTEIN S DEFICIENCIES

To the Editor:

Protein S is a vitamin K-dependent plasma protein that serves as a cofactor for the anticoagulant reaction catalyzed by activated protein C. Genetic disorders involving low levels of protein S are associated with thrombotic conditions; acquired deficiency of protein S has been reported during pregnancy, disseminated intravascular coagulation, liver disease, nephrotic syndrome, systemic autoimmune diseases, and human immunodeficiency virus (HIV). Spontaneously occurring antibodies to the natural inhibitors of blood coagulation have been already described. Particularly, antibodies directed against a combination of phospholipids with prothrombin, protein C, or protein S have been proposed to play a role in the mechanism causing thrombosis. Recently, D'Angelo et al reported one case of autoimmune protein S deficiency in a boy with severe thromboembolic disease, demonstrating that the inhibition of protein S activity was related to anti-protein S–specific antibodies.

We have performed an investigation with the aim to evaluate the presence of specific anti-protein S antibodies in acquired protein S deficiencies. Plasma from 19 patients with protein S deficiency (<70 U/dL) positive for the lupus anticoagulant (LAC), from 24 patients with protein S deficiency in HIV infection, and from 40 matched healthy blood donors were tested. Protein S antibodies were detected by immunoblotting, using 0.8 µg of purified protein S (Boehringer Mannheim, Inc., Germany). After running on a discontinuous slab gel composed of a 4% stacking gel and a 10% running gel, gels were transferred to nitrocellulose. It was subsequently incubated for 1 hour in 0.02 mol/L Tris (0.5 mol/L NaCl, pH 7.5) containing 1% albumin. Sera were diluted 1/100 in the same buffer. After washing, the nitrocellulose was incubated for 1 hour in horseradish conjugate goat antihuman IgG, diluted 1:100 in TBS-albumin, and developed by adding of 4 chloro-1-naphthol.

Our findings showed that anti-protein S antibodies were present in a large proportion of patients with acquired protein S deficiency.
Table 1. Occurrence of Anti-Protein S Antibodies

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. Positive</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired PS deficiency LAC↑</td>
<td>10/19*</td>
<td>52.6</td>
</tr>
<tr>
<td>Acquired PS deficiency HIV Ab↑</td>
<td>9/24*</td>
<td>37.5</td>
</tr>
<tr>
<td>Healthy blood donors</td>
<td>0/40</td>
<td>0</td>
</tr>
</tbody>
</table>

* P < .001 versus healthy blood donors.

(Table 1). By contrast, none of the plasmas of 40 healthy blood donors showed the presence of anti-protein S antibodies.

The presence of specific antibodies to protein S in a large proportion of patients with clearly decreased levels of protein S activity supports the pathogenic role of an (auto)immune response in many acquired protein S deficiencies.

A follow-up study is in progress with the aim to evaluate the risk of developing thrombotic manifestations in patients with anti-protein S autoantibodies.

Maurizio Sorice
Tamara Griggi
Annapia Circella
Luisa Lenti
Dip. Medicina Sperimentale
Paolo Arcieri
Gian Domenico Di Nucci
Guglielmo Mariani
Centro Trombosi, Dip. Biopat. Umana
Università “La Sapienza”
Rome, Italy

REFERENCES


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M Sorice, T Griggi, A Circella, L Lenti, P Arcieri, G Domenico di Nucci and G Mariani

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