Prothrombotic States in Young People With Idiopathic Stroke
A Prospective Study

Fernando Barinagarrementeria, MD; Carlos Cantú-Brito, MD; Aurora De La Peña, MSc; Raúl Izaguirre, MD

Background and Purpose Although 4% of cerebral infarcts in the young can be attributed to hematologic disturbances that predispose to thrombosis, the frequency of cerebral infarcts caused by prothrombotic states is not known. Recently, the association between cerebral infarction and deficiencies of elements of the natural anticoagulant system has been recognized.

Methods Thirty-six consecutive patients under 40 years of age with cerebral infarction of undetermined cause were prospectively studied. Quantitation of natural anticoagulants was done at least 3 months after the cerebral infarction. The following activity tests were performed, all by the chromogenic method: antithrombin III, protein C, plasminogen, tissue plasminogen activator, and inhibitor of tissue plasminogen activator. Protein S was quantified by the Laurell rocket method. All patients underwent a complete cardiological examination, including two-dimensional echocardiography, as well as four-vessel cerebral angiography. Some patients were also studied by transesophageal echocardiography.

Results Of 36 patients, 17 were male, with a mean age of 28 years. Mean age for women was 25 years. Nine patients (25%; 5 women, 4 men) had a deficiency of one natural anticoagulant and constituted group I. In these patients, isolated protein S deficiency was detected in five cases (13.8%); in one case, we observed the association between protein S deficiency and antiphospholipid antibodies; and deficiency of protein C was seen in one case (2.7%), of antithrombin III in one case (2.7%), and of plasminogen in one case (2.7%). Instances of cerebral infarction without natural anticoagulant deficiency (group II) included 12 women and 15 men. There were no differences in clinical and radiological findings between the two groups.

Conclusions Considering the importance of prothrombotic state, especially caused by deficiency of protein S, in the development of cerebral infarcts, we suggest that it should be looked for in every young patient affected by this pathological entity and in whom no etiologic factors can be determined. (Stroke. 1994;25:287-290.)

Key Words • anticoagulants • proteins • thrombosis • young adults

Subjects and Methods
Thirty-six consecutive patients under 40 years of age who had an arterial cerebral infarction of undetermined cause were prospectively selected over a 2-year period from the stroke clinic of a third-level facility hospital. We considered the cause of infarction as being undetermined when no cardiac embolic source (we did not exclude patients with mitral valve prolapse or patent foramen ovale because of their controversial role as embolic sources), or nonatherosclerotic (arterial dissection, fibromuscular dysplasia) or atherosclerotic vasculopathies were found after exhaustive studies were completed. Cerebral infarctions were demonstrated by computed tomographic (CT) scanning and/or magnetic resonance imaging. Laboratory examinations included full blood count, blood levels of glucose, creatinine and urea, lipid profile including lipoproteins, hepatic and renal function tests, rheumatologic profile including antiphospholipid antibodies, coagulation tests including D-dimers and fibrinogen split products, VDRL, erythrocyte sedimentation rate, chest x-rays, and tests for tuberculosis and cystercerosis on cerebrospinal fluid. All patients underwent a complete cardiological examination, including two-dimensional echocardiography as well as four-vessel cerebral angiography. Some patients were also studied by transesophageal echocardiography.

Patients who had transient cerebral or retinal ischemia, cerebral venous thrombosis, abnormal coagulation tests, or hepatic disease or who were on anticoagulant therapy were excluded.

Quantitation of natural anticoagulants was done at least 3 months after the cerebral infarction. The following activity
tests were performed, all by the chromogenic method (Kabi-Vitrum, Stockholm, Sweden): antithrombin III (AT-III), protein C, plasminogen, tissue plasminogen activator (TPA), and inhibitor of TPA. Protein S was quantified by the Laurell rocket method (American Diagnostica Inc, Greenwich, Conn). Test results for protein C antigen and free protein S were expressed in relative percentages. The same tests were performed in 38 healthy individuals who were first-time blood donors, matched for age and sex. Normal values represent those prospectively derived from the age-matched control group. The tests were performed in both patients and control subjects simultaneously. Normal values in our laboratory were as follows: protein C, 64% to 127% of activity; AT-III, 71% to 125% of activity; plasminogen, 75% to 115%; TPA, 1.28 to 4.12 IU; TPA inhibitor, 0.5 to 40.1 U; and protein S, 50% to 140%. A result more than 2 SDs from the mean value was considered abnormal. In those patients who had a decrease of activity of any element, antigenic assays were done by the method of radial immunodiffusion (Behring Diagnostica). In patients with deficiency of natural anticoagulants, another determination was performed to confirm the abnormality. Antiphospholipid antibody determinations were performed in all patients. In cases of deficiency of natural anticoagulants, we studied members of the patients' families. The clinical and radiological evolution of the patients with deficiency of natural anticoagulants (group I) was compared with that of patients with cerebral infarct without thrombophilic abnormalities (group II). All patients were followed for at least 12 months. The statistical analysis was performed using $2 \times 2$ contingency tables and validation by the $x^2$ test and Fisher's exact test.

## Results

Of 36 patients, 17 were male, with a mean age of 28 (range, 16 to 40) years. Mean age for women was 25 (range, 10 to 40) years. Nine patients (25%; 5 women, 4 men) had a deficiency of one natural anticoagulant and constituted group I. In these patients, isolated protein S deficiency was detected in 5 cases (13.8%), and in 1 case we observed the association between protein S deficiency and antiphospholipid antibodies (3 men, 3 women); deficiency of protein C was seen in 1 case (2.7%), of AT-III in 1 case (2.7%), and of plasminogen in 1 case (2.7%). Instances of cerebral infarction without natural anticoagulant deficiency (group II) included 12 women and 15 men ($P=.7$).

Regarding the medical histories of both groups (Table 1), the only difference was a much higher incidence of smoking (44.4%) among members of group I compared with that of group II patients (7.4%, $P=.002$). Echocardiographic abnormalities were present in 44.4% of the group I patients: there were 3 instances of mitral valve prolapse and 1 of patent foramen ovale. This contrasted with an incidence of only 14.8% in group II patients (1 occurrence of mitral valve prolapse and 1 of patent foramen ovale). However, the difference was not significant ($P=.08$). Both groups had CT scan findings of a similar nature. Twenty of 36 patients (55.5%) had some intracranial abnormality detected by cerebral angiography: occlusion in 9, stenosis in 2, vessel irregularities in 8, and distal occlusion in 1. Neuroimaging studies were not useful to determine the etiology of the cerebral infarcts in either group. Nine patients underwent follow-up angiographic examination; in 3 of 4 patients from group I, there was progression (increasing stenosis or occlusion) of the arterial lesions, whereas this was seen in only 1 of 5 group II patients. This particular patient had borderline values of AT-III.

During the follow-up period, no instances of recurrence were observed. Measurements of natural anticoagulants were performed in 22 relatives of 6 of the 9 patients with abnormalities. Protein S deficiency was detected in 5 of 10 relatives of 1 patient with protein S deficiency. The tests were normal in the other 12 relatives from the remaining 5 families.

## Discussion

There is much controversy regarding the role of prothrombotic state as a cause of cerebral infarction of arterial type, and until now, few studies have analyzed the relationship between these two conditions.

In one fourth of our 36 patients, there was a deficiency of one of the natural anticoagulants, most commonly type II deficiency of protein S. Protein S is a vitamin K-dependent plasma protein functioning as a cofactor for the anticoagulant activity of activated protein C. Deficiency of protein S has autosomal dominant inheritance. Protein S occurs in both free and bound (functionally inactive) forms. Hereditary deficiency of protein S results in a prothrombotic state. There are two main protein S-deficiency types: type I, in which there is deficiency of free and bound protein S; and type II, in which the free fraction is decreased, with the total concentration of protein S normal. Our results differ from those of Chancellor and coworkers, who found no hematologic abnormality in 38 patients with cerebral infarction of undetermined etiology. Recently, Martinez et al. discovered an incidence of 16% of prothrombotic state in Mexican youths with cerebral infarcts of various etiologies. Sacco et al. found a deficiency of protein S in 8 of 35 patients under 40 years of age with idiopathic infarcts. Our series is very similar to the latter, possibly because both included young (under 40 years) patients with idiopathic cerebral infarcts (Table 2).

In other reports, there was a higher incidence of this association among women, in a proportion of 2:1. The explanation was offered that the use of oral contraceptives could favor thrombosis. In addition, prolapse of the mitral valve is a common finding among asymptomatic women. In our series, there were no differences of incidence relating to sex.

### Table 1. History In Patients With and Without Prothrombotic State and Stroke

<table>
<thead>
<tr>
<th>Finding</th>
<th>Group I (n=9)</th>
<th>Group II (n=27)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial stroke</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>4*</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Migraine</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Extracerebral thrombosis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Recurrence stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Past stroke</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Group I indicates patients with prothrombotic state; Group II, patients without prothrombotic state. $P=.02$. 

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The habit of smoking was more prevalent among group 1 members. In a recent article, Scott et al.\(^{23}\) showed a decrease of protein S in smoking men and suggested that this might explain the thrombotic complications associated with this habit.

Deficiency of one of the natural anticoagulants seems to precipitate thrombogenesis in the presence of a minor triggering factor.\(^{24}\) In our study, approximately half of group 1 had a potentially embolicogenic cardiac abnormality, detected by echocardiography.\(^{25}\) Possibly, the association of minor risk factors in the presence of prothrombotic states may elevate the risk of a cerebral infarct. An example of this is the case reported by Wallis and Godwin,\(^{26}\) that of a 21-year-old woman with cerebral ischemia associated with protein S deficiency, cigarette smoking, use of oral contraceptives, and mitral valve prolapse.

Most hereditary clotting deficits manifest as peripheral venous, rather than arterial, thrombosis.\(^{27-29}\) Venous thrombosis in unusual sites suggests a previous prothrombotic state.\(^{30}\) There was no previous personal or family history of thrombosis in any of the group I patients or in any of the cases reported by Martinez et al.\(^{19}\) Cerebral infarcts can therefore be the first clinical manifestation of a prothrombotic state.

Recently, several articles have been published in which prothrombotic state is associated with cerebral vascular disease.\(^{31-37}\) The time of the measurement is important. Mayer et al.\(^{38}\) have demonstrated low values of protein S in patients with acute stroke as well as in hospitalized control patients, even in the absence of a recognized predisposing condition; such abnormality has been related to a decrease in the ratio of free protein S to bound protein S (C4b-BP). C4b-BP is an acute phase protein, and during inflammatory response its concentration may be increased up to 400% of normal.\(^{39}\) The causal role of a prothrombotic state has been associated with the persistence of the abnormality; for this reason it is recommended to perform these tests several months after the acute stroke. Specific tests to detect these uncommon disorders are expensive and unavailable in many countries, especially those in developing areas of the world. Manucci and others\(^{40,41}\) have suggested the step procedure for the diagnosis of the hypercoagulable states in the laboratory. As a first step, it is recommended to perform functional assays, and the chromogenic methods are more sensitive than coagulometric ones. According to this recommendation, we performed chromogenic assays in our study. The detection of protein S in the laboratory is complicated in that there are no commercially available functional assays. Among the several methods, immunodiffusion assay (Laurell rocket method) is recommended.\(^{20}\) If a physician has to limit the number of such tests, he will have to try to detect by clinical means the patients in whom tests could be most useful. It is our impression that except for the habit of smoking, no clinical or radiological data allow the physician to identify the subjects with possible prothrombotic state among those with cerebral infarction of undetermined cause.

Four patients with angiographic evidence of arterial intracranial occlusion were given the same examination several months after the infarction. Vascular obliteration progressed in three, whereas there were no changes in the fourth subject. This suggests that in prothrombotic states there might be a permanent thrombogenic stimulus that leads to progressive intracranial thrombosis; however, this hypothesis has to be tested further.

On analyzing eight series (including the present one)\(^{19-19}\) that deal with the association of prothrombotic states and arterial cerebral infarction, deficiency of natural anticoagulants was found in 52 of 311 cases (16.7%). In order of frequency, this deficiency involved protein S (71%), AT-III (13%), protein C (13%), and plasminogen (1 case).

Considering the importance of prothrombotic state, especially caused by deficiency of protein S, in the development of cerebral infarcts, we suggest that it should be looked for in every young patient affected by this pathological entity and in whom no etiologic factors can be determined.

**References**


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**Table 2. Series of Patients With Stroke and Prothrombotic States**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (No.)</th>
<th>Age</th>
<th>Characteristics</th>
<th>Cerebral Infarct</th>
<th>Deficiencies</th>
<th>Patients With Deficiencies</th>
<th>AT-III</th>
<th>PC</th>
<th>PS</th>
<th>Plasminogen</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Angelo</td>
<td>1988</td>
<td>37</td>
<td>WL</td>
<td>First hours</td>
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<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>NM</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Safer</td>
<td>1989</td>
<td>33</td>
<td>WL</td>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>Prospective</td>
</tr>
<tr>
<td>Chancellor</td>
<td>1989</td>
<td>38</td>
<td>&lt;40</td>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Sacco</td>
<td>1989</td>
<td>35</td>
<td>&lt;40</td>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>Prospective</td>
</tr>
<tr>
<td>Camerlingo</td>
<td>1991</td>
<td>50</td>
<td>&lt;45</td>
<td>Cerebral Infarct</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>6</td>
<td>NM</td>
<td>3</td>
<td>Prospective</td>
</tr>
<tr>
<td>Green</td>
<td>1992</td>
<td>22</td>
<td>WL</td>
<td>Cerebral Infarct</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>44</td>
<td>1</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Martinez</td>
<td>1993</td>
<td>60</td>
<td>&lt;45</td>
<td>Cerebral Infarct</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>16</td>
<td>5</td>
<td>3</td>
<td>Prospective</td>
</tr>
<tr>
<td>Present series</td>
<td>1993</td>
<td>36</td>
<td>&lt;40</td>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>25</td>
<td>1</td>
<td>6</td>
<td>Prospective</td>
</tr>
</tbody>
</table>

AT-III indicates antithrombin III; PC, protein C; PS, protein S; WL, without age limit; NM, not measured; Idiopathic, without some specific etiology; and Cerebral Infarct, with and without defined etiology.


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