Ischemic Stroke Due to Deficiency of Coagulation Inhibitors
Report of 10 Young Adults

Hector R. Martinez, MD; Ricardo A. Rangel-Guerra, MD, FACP; and Luis J. Marfil, MD

Background and Purpose: Deficiencies in coagulant inhibitors protein C, protein S, and antithrombin III increase the risk of venous thrombosis. We describe 10 young adults with cerebral arterial thrombosis due to deficiencies in these factors.

Methods: Sixty patients younger than 45 years were hospitalized because of acute ischemic stroke diagnosed through computed tomography or magnetic resonance imaging. Cerebral angiography was performed in 54 cases. Hematologic and coagulation profiles, autoantibody screen, syphilis serology, and lupus anticoagulant were analyzed in all patients. Among the total cases, Holter monitoring was performed in 13 patients, echocardiography in 20, and cerebrospinal fluid studies for cysticercosis and tuberculosis in two. The quantitative analysis of protein C, protein S (by Laurell rocket immunoelectrophoresis), and antithrombin III (by radial immunodiffusion) was performed on admission and 3 months after stroke in all patients and in relatives of six patients.

Results: In 10 cases (17%) the stroke was attributed to deficiency of coagulation inhibitors: three men had protein C deficiency, two women had protein S deficiency, and five had antithrombin III deficiency (three men and two women). The cerebral infarction involved the carotid territory in these 10 patients. None had previous thromboembolic disease. Eight patients showed a complete recovery. An acquired disorder was presumed in one protein S-deficient and in two antithrombin III-deficient patients; the remainder were considered heterozygous.

Conclusions: The cerebral vasculature may be primarily involved in the deficiency of these natural anticoagulants. Young adults seem to be the most often affected. A knowledge of these new clotting defects will enable the clinician to improve the prevention and treatment of this devastating neurological disease. (Stroke 1993;24:19-25)

Key Words • blood coagulation • cerebral ischemia • young adults

In about 4% of young adults with cerebral infarction, the major precipitant to thrombosis is a hematologic abnormality.1,2 This rate probably underestimates the role of hemostatic disturbances as a cause of cerebrovascular events. Atherosclerosis is an uncommon cause of cerebral infarct in young adults.3 Cardioembolism is generally regarded as the most important cause of ischemic stroke in this age group.4,5 The etiology of the cerebral infarction remains unexplained in a significant number of young patients even after extensive investigation.6,7

In acute ischemic stroke, usually no abnormalities are found in the routine hematologic or coagulation tests.8 Some authors have reported the occurrence of hemostatic disturbances in young stroke patients, such as abnormalities of platelet function, coagulation inhibition, and/or fibrinolysis.9-12 Naturally occurring coagulation inhibitory proteins (CIP) have recently been clarified. These CIP include antithrombin III (ATIII), protein C (PC), and protein S (PS).13-15 At the present time the natural anticoagulant pathway is becoming better appreciated and understood in the regulation of thrombosis. Although CIP deficiency usually causes venous thrombosis, it has been reported recently that cerebral arteries may be primarily involved.16-19

The CIP inhibit clotting mechanisms acting in different ways. ATIII binds to heparan on the surface of endothelial cells, increasing its ability to inhibit thrombin and other activated clotting factors.20-22 PC is an anticoagulant protease that after activation by the reaction of thrombin with thrombomodulin on the endothelial cell surface inactivates thrombin and activated factors V and VIII and also promotes fibrinolysis. PS is found free in plasma and bound to an inhibitory protein of the complement system. Only the free form accelerates PC inhibition of the activated factors V and VIII.

Several reports have implicated PC or PS deficiencies in the etiology of ischemic stroke.16-19 Documented cerebral arterial thrombosis due to ATIII deficiency has been reported in a small number of cases, with a preponderance of inherited causes.23,24 In this article we describe 10 young adults with acute ischemic stroke secondary to deficiency of the CIP. Deficiency of ATIII...
was found in five patients, three patients had PC deficiency, and two showed PS deficiency.

Subjects and Methods

Between April 1988 and March 1992, 60 patients (37 men, 23 women) younger than age 45 years were hospitalized within 48 hours of their first ischemic stroke. Patients with diagnosis of complicated migraine, transient ischemic attacks, and intracerebral or subarachnoid hemorrhage were excluded. All patients had their diagnosis confirmed on admission either by cranial computed tomography (CT scan) or magnetic resonance imaging (MRI). A four-vessel cerebral angiography was performed in 54 cases.

A clinical profile was obtained in each patient recording the personal history of hypertension, cardiac disease, diabetes, migraine, family history of premature vascular disease, intake of oral contraceptives, drug intake, and smoking. The relation of acute stroke to pregnancy, alcohol consumption, or preceding viral infection was also noted. None of the patients received anticoagulant treatment before or during hospitalization. The therapy in all cases consisted of maintenance of adequate blood pressure, osmotic therapy with either mannitol or glycerol, and use of antiplatelet drugs (ticlopidine or aspirin) when no contraindication was present.

All patients had an electrocardiogram and chest x-ray. M-mode and two-dimensional echocardiography was performed in 20 patients, 24-hour Holter monitoring in 13 patients, and color Doppler of the carotid arteries and transcranial Doppler in 15 patients. Routine hematologic profiles including blood count, platelet count, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, biochemistry profile (glucose, blood urea nitrogen, creatinine, albumin, bilirubin, and cholesterol), syphilis serology, autoantibody screen, fibrinogen, and lupus anticoagulant were analyzed in all patients. Immunologic studies for tuberculosis and cisticercosis in cerebrospinal fluid were performed in two cases.

The CIP were determined within 48 hours from the onset of symptoms and before any treatment was started. Venous blood samples were obtained from an antecubital vein of the nonparalyzed arm by means of clean venipuncture using an evacuated tube containing 0.129 M sodium citrate as an anticoagulant. The sample was centrifuged at 1,600–2,000g for 10 minutes, and the plasma was stored at −70°C until assayed.

The quantitative study of PC antigen and free PS antigen (after separation and precipitation of bound PS with polyethylene glycol) was performed immunologically by Laurell rocket electrophoresis using sheep or goat antiserum to human PC or human PS, respectively.25 These antibodies were obtained from Helena Laboratories, Beaumont, Tex., and were incorporated into agarose in tris(hydroxymethyl)aminomethane (Tris)-tricine buffer. The results for PC antigen and free PS antigen were expressed as the relative percentage compared with a pooled normal plasma standard. The expected normal range for PC antigen was 65–145%, and the coefficient of variation (CV) for this assay was 3.0% in a within-run reproducibility study. The normal range for free PS antigen was 60–150% with a CV of 5.2% in a within-run reproducibility study performed in five donor samples. The quantitative analysis of ATIII was performed by radial immunodiffusion26 using goat anti-human ATIII (Helena) added to the agarose. The results were reported in milligrams per deciliter; the normal range obtained in our laboratory was 9–14 mg/dl. Within-run reproducibility was determined performing an ATIII assay on 10 donor samples; the CV obtained was 4.1%.

All patients had a follow-up of at least 6 months. At a 3-month interval another determination of PC, PS, and ATIII was performed in those patients with deficiency in these factors. The CIP were determined in relatives of two patients with PC deficiency (two brothers and the father of patient No. 1 and three children of patient No. 2), in relatives of the two patients with PS deficiency (in the newborn of patient No. 4; in the son, two sisters, one brother, and parents of patient No. 5), and in relatives of two patients with ATIII deficiency (four brothers of patient No. 3 and four sisters of patient No. 8).

Results

In one third of the 60 patients the probable etiology of the cerebral infarct was undetermined. Four patients died within 3 months of their cerebrovascular event, two of systemic medical complications and two of underlying heart or vascular diseases (myocardial infarction and Takayasu’s disease). Fifty-five patients (92%) had cerebral infarction in the carotid territory and five in the brain stem (two with lateral medullary infarct, two with lateral pontine infarct, and one with mesencephalic infarct). The infarct was demonstrated on CT in 52 patients and by MRI in the remaining eight.

In 10 patients (17%) the acute ischemic stroke was attributed to a hematologic disorder. This group of patients comprised six men and four women, with a mean age of 31.4 years (range, 24–38 years); there was no significant difference in mean age between women and men. Table 1 summarizes the clinical features of these 10 patients at the time of admission. Cerebral angiography was performed in nine patients, which showed either an occluded vessel or partial filling intravascular defect in eight. Four of these patients had unilateral internal carotid artery occlusion (Figure 1). In one case the angiogram was normal and free of atherosclerosis. The median interval from the ictus to angiography was 5 days. The MRI demonstrated isointense or hypointense lesions on T1-weighted images (Figure 2, left panel) and hyperintense lesions on T2-weighted images (Figure 2, right panel and Figure 3, left panels) corresponding to the occluded vessels in all cases. The CT was normal in one of nine patients. The carotid territory was involved in these 10 cases.

The routine hematologic tests were normal in the 10 reported cases. The immunologic studies in cerebrospinal fluid for cisticercosis and tuberculosis performed in two patients were also normal. The antinuclear and anticardiolipin antibodies were positive in only one patient (No. 5). The quantitative analysis of the CIP showed ATIII deficiency in five patients, PC deficiency in three men, and PS deficiency in two women. None of these patients had previous systemic venous thrombosis.

Eight patients had associated clinical conditions that probably promoted stasis or a prothrombotic state. Of the three men with cerebral infarction secondary to PC
TABLE 1. Clinical Profiles of 10 Patients With Acute Ischemic Stroke Attributed to Hematologic Disorder

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Clinical features</th>
<th>CT/MRI/CA</th>
<th>CIP deficiency*</th>
<th>CIP follow-up†</th>
<th>Associated disorder</th>
<th>Venous thrombosis</th>
<th>Family history</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/26/M</td>
<td>Right hemiparesis, sensory transcortical aphasia</td>
<td>N/A/A</td>
<td>Protein C (25.9%)</td>
<td>Protein C (50%)</td>
<td>Respiratory disease</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>2/33/M</td>
<td>Right hemiparesis, aphasia, seizures</td>
<td>A/A/A</td>
<td>Protein C (10%)</td>
<td>Protein C (35%)</td>
<td>Heavy smoking</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>3/34/M</td>
<td>Left hemiparesis</td>
<td>A/A/A</td>
<td>ATIII (6.8 mg/dl)</td>
<td>ATIII (10 mg/dl)</td>
<td>Heavy alcoholism</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>4/28/F</td>
<td>Left hemiparesis, seizures</td>
<td>A/A/NP</td>
<td>Protein S (16%)</td>
<td>Protein S (40%)</td>
<td>Puerperium, juvenile diabetes</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>5/28/F</td>
<td>Left hemiplegia</td>
<td>A/A/A</td>
<td>Protein S (35%)</td>
<td>Protein S (60%)</td>
<td>Oral contraceptives, rheumatoid arthritis</td>
<td>Negative</td>
<td>Negative</td>
<td>Left hemiplegia</td>
</tr>
<tr>
<td>6/24/M</td>
<td>Seizures, lower left monoparesis</td>
<td>A/A/A</td>
<td>ATIII (4.2 mg/dl)</td>
<td>ATIII (9.6 mg/dl)</td>
<td>Obesity</td>
<td>Negative</td>
<td>Negative</td>
<td>Left monoparesis</td>
</tr>
<tr>
<td>7/31/F</td>
<td>Complex partial seizures, right homonymous hemianopia</td>
<td>A/A/A</td>
<td>ATIII (2 mg/dl)</td>
<td>ATIII (4 mg/dl)</td>
<td>Obesity, juvenile diabetes</td>
<td>Negative</td>
<td>Negative</td>
<td>Complex partial seizures</td>
</tr>
<tr>
<td>8/37/F</td>
<td>Agnosia, acaulcia, right homonymous hemianopia, headache</td>
<td>A/A/A</td>
<td>ATIII (4 mg/dl)</td>
<td>ATIII (4.8 mg/dl)</td>
<td>None</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>9/38/M</td>
<td>Right cerebellar ataxia, right dysmetria</td>
<td>A/A/A</td>
<td>ATIII (4.8 mg/dl)</td>
<td>ATIII (6.5 mg/dl)</td>
<td>None</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
<tr>
<td>10/35/M</td>
<td>Right homonymous hemianopia</td>
<td>NP/A/N</td>
<td>Protein C (50%)</td>
<td>Protein C (55%)</td>
<td>Heavy alcoholism</td>
<td>Negative</td>
<td>Negative</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

Pt, patient; CT, computed tomography; MRI, magnetic resonance imaging; CA, four-vessel cerebral angiography; CIP, coagulation inhibitory proteins; M, male; F, female; N, normal; A, abnormal; NP, not performed; ATIII, antithrombin III.

†Performed at 3 months after the stroke.

Ischemic stroke started in the postpartum period in a woman with a history of juvenile diabetes; the other had a history of rheumatoid arthritis and had used oral contraceptives during the 2 years before her clinical event. In patients with ATIII deficiency, one had a respiratory tract infection with hyperthermia 2 days before his clinical event; heavy smoking was noted in one, and the other had a history of excessive alcohol consumption during the 2 days preceding the stroke. In patients with PS deficiency, the

FIGURE 1. Cerebral angiography showing occlusion of right middle cerebral artery in a patient with protein S deficiency (arrow) (patient No. 5) (left panel) and occlusion in origin of left internal carotid artery in a patient with protein C deficiency (arrow) (patient No. 1) (right panel).
history of heavy alcohol consumption several days before his stroke, and two patients were obese, one of whom had juvenile diabetes (No. 7). No associated clinical conditions were observed in the other two patients with ATIII deficiency.

The measurements of PC, PS, and ATIII were normal in all the relatives studied. All patients were treated with antiplatelet drugs, with complete recovery in eight. MRI follow-up showed a decrement in size of the lesion in these subjects (Figure 3, right panels). There was no mortality; morbidity was present in two subjects, one with PS deficiency (left hemiplegia) and one with ATIII deficiency (lower left monopareshis). No correlation was observed between morbidity, outcome, and the proportion of CIP deficiency.

The determinations of CIP at 3 months after the stroke showed that the values remained low in subjects with PC deficiency, in one patient with PS deficiency, and in three ATIII-deficient patients (Table 1). In one patient (No. 5) with PS deficiency and in two patients with ATIII deficiency (No. 3 and No. 6) the values returned to normal at 3-month follow-up.

**Discussion**

The etiology of stroke in young adults remains undetermined in a significant number of cases. In this age group, a hematologic disorder is the etiology of the stroke in approximately 4% of cases. More complete laboratory screening of stroke patients for currently identified prothrombotic states will probably increase the rate of strokes attributed to these disorders; thus, the underestimated role of hematologic disease as a cause of cerebrovascular events may change in the near future.

In acute ischemic stroke, the routine hematologic or coagulation tests are usually normal. The recognition of the naturally occurring CIP, such as ATIII, PC and PS, and the fibrinolytic system, have increased our knowledge in relation to hemostatic abnormalities that may promote thrombosis and thereby contribute to stroke.

In 21 patients (35%) the etiology of the stroke remained undetermined. A hematologic disorder was implied as the etiology of the cerebral infarct in 10 subjects (17%). Our rate of stroke of unexplained origin appears to be lower than that in other reports in this age group. The high incidence of hematologic diseases may reflect a selection bias in the present series.

In contrast with other reports that failed to document deficiencies in the CIP in stroke patients, we found PC deficiency in three men, PS deficiency in two women, and ATIII deficiency in two women and three men. All these subjects were negative for hypertension, hyperlipidemia, valvular or ischemic cardiac disease, and transient ischemic attacks. Atherosclerosis, carotid or vertebral dissection, and fibromuscular dysplasia were excluded by means of cerebral angiography. Other etiologies commonly observed in our country such as cysticercosis and tuberculosis were excluded through immunologic cerebrospinal fluid studies. No abnormalities were observed in the routine coagulation profile. Lupus anticoagulant was negative in all patients, whereas antinuclear antibodies were positive in a patient with a history of rheumatoid arthritis (No. 5), which was inactive at the onset of the cerebrovascular event.

In patients with PC deficiency there was an associated disorder that acted in synergy with this deficient protein and may have promoted thrombosis in cerebral vasculature. PC is a vitamin K-dependent zymogen of a plasma serine protease. After in vivo activation by the reaction of thrombin with endothelial thrombomodulin, it inhibits blood coagulation by inactivating factors Va and VIIIa. It is also involved in the regulation of
the fibrinolytic system by neutralizing the activity of plasminogen activator inhibitors and possibly causing release of tissue plasminogen activator. There are two types of deficiency: type I (reduction in concentration and functional activity) and type II (normal concentration and reduction in functional activity).

PC deficiency is inherited as an autosomal dominant trait with incomplete penetrance. Heterozygous persons have an increased risk of venous thrombosis and thromboembolism at a young age. Recent reports have described a primary involvement of cerebral vasculature in PC-deficient patients. The patients described in this article have not experienced previous systemic thromboembolic complications. When a hematologic abnormality is identified in acute ischemic stroke, it cannot be assumed to antedate stroke. Support for an antecedent, causal role of the hematologic disorder includes its persistence in subsequent months or identification of the abnormality in family members. The screening performed in relatives of two PC-deficient subjects revealed normal values. We consider that the patients reported in this article are heterozygous persons in whom the associated clinical condition made this deficiency clinically evident. The values obtained 3 months after the stroke confirm that the PC deficiency was present before the cerebrovascular event and that it was not the consequence of the cerebral infarct.

In PS-deficient patients, one subject had her cerebrovascular event in the puerperium and the other woman was using oral contraceptives during the 2 years previous to the stroke. These clinical conditions may produce a reduction in free PS levels and consequently an overactivity of the coagulation system.

The PS is synthesized by hepatic cells and endothelium. It is found free in plasma and bound to C4b-binding protein, an inhibitory protein of the comple-

**FIGURE 3.** Coronal (upper left panel) and axial (lower left panel) magnetic resonance images showing a high-intensity signal in left parietal lobe corresponding to ischemic infarction in a patient with protein C deficiency (T2-weighted image; echo time, 2,000 msec; repetition time, 85 msec). Coronal (upper right panel) and axial (lower right panel) magnetic resonance images from the same patient, obtained 3 months after the acute stroke. Coronal: echo time, 2,000 msec; repetition time, 28 msec. Axial: echo time, 2,000 msec; repetition time, 85 msec.
Hematologic causes of ischemic stroke are most often described in young adults. In this age group the atherosclerotic mechanisms are less likely than in older patients. When a hematologic abnormality is identified after a cerebrovascular event, it cannot be assumed to antedate stroke. To support antedating, the abnormality should remain present in the following months or be present in family members. In our patients, the values of PC (three patients), PS (one patient), and ATIII (three patients) remained low at 3 months after the stroke, supporting the hypothesis that these deficiencies were the cause rather than the consequence of the stroke. An understanding of clotting mechanisms and the more complete laboratory screening performed in stroke patients should permit recognition of more hematologic abnormalities as a cause of cerebral infarct. A knowledge of these new pathophysiological mechanisms will enable the clinician to improve the prevention and treatment of this devastating neurological disease.

References
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