We describe two adult patients who presented with acute cerebral infarction and were found to have a hypercoagulable state due to nephrotic syndrome. One patient had a deficiency of free protein-S. The other patient had a pulmonary embolus 4 months after the stroke. Our cases demonstrate that the hypercoagulable state associated with nephrotic syndrome can be associated with cerebral arterial thrombosis and infarction in adults. Examination of the urine remains an important part of the evaluation of patients with recent stroke. The presence of severe proteinuria and a low serum albumin content should prompt consideration of a hypercoagulable state. Our experience suggests that anticoagulant drugs may be required to reduce the risk of new thrombotic events. (Stroke 1991;22:90–93)

While ischemic stroke frequently results from atherothrombotic or cardioembolic arterial occlusions, a number of other conditions can predispose to arterial thrombosis. We recently studied two patients who presented with acute ischemic stroke and were subsequently found to have a hypercoagulable state resulting from nephrotic syndrome.

**Case Reports**

**Case 1**

A 36-year-old previously healthy man was transferred to the University of Iowa Hospitals shortly after the onset of right-sided weakness and the inability to talk. He did not have a history of cigarette smoking, alcohol consumption, or use of illicit drugs. There was no family history of stroke, heart disease, or other thrombotic disorders. On admission he had a global aphasia, right hemiparesis, right homonymous hemianopsia, and decreased sensory perception on the right. Carotid pulses were symmetrical, and there were no bruits. Cardiac examination was normal. He had no evidence of systemic embolization, peripheral edema, or deep-vein thrombosis.

Computed tomography demonstrated an evolving ischemic infarct in the distribution of the left middle cerebral artery. A cerebral arteriogram demonstrated complete occlusion of the left middle cerebral artery (Figure 1). The proximal carotid and other intracranial vessels were normal. Laboratory studies included a normal complete blood count, normal concentrations of electrolytes, blood urea nitrogen, and creatinine, and normal serum chemistries. The total serum protein concentration was 4.1 (normal range 6–8) g/dl, and the serum albumin concentration was 2.4 (normal range 3.3–5) g/dl. Urinalysis revealed a high specific gravity of 1.027 and 3+ protein. Serum complement studies demonstrated a C3 concentration of 76 (normal range 70–176) mg/dl and a decreased C4 concentration of 9 (normal range 16–45) mg/dl. His evaluation also included a normal chest roentgenogram, a normal electrocardiogram, normal cardiac monitoring, and normal transthoracic, contrast, and transesophageal echocardiograms. Venous Doppler study of the lower extremities was unremarkable. A 24-hour urine protein content was elevated at 11.4 (normal value <0.1) g. Prothrombin time, partial thromboplastin time, and thrombin time were normal. Fibrinogen concentration was increased to 701 (normal range 160–340) mg/dl. He had normal antithrombin-III, total protein-S, and protein-C concentrations. Plasminogen content was increased to 145% (normal range 90–110%). Free protein-S content was decreased to 55% (normal range 60–140%). Other studies included a nonreactive VDRL and negative assays for antinuclear antibodies, anticardiolipin antibodies, neutrophil cytoplasmic antibody, and cryoglobulins. Blood cultures were negative.

His nephrotic-range proteinuria was believed to be secondary to a membranoproliferative glomerulonephritis although a renal biopsy was not obtained. Because of the presumptive hypercoagulable state...
secondary to nephrotic syndrome, he was treated with heparin followed by warfarin. His clinical condition gradually improved, but he had a residual aphasia and right hemiparesis at the time of discharge.

Case 2

A 34-year-old man was transferred to the University of Iowa Hospitals 2 days after the onset of difficulty driving followed by a severe right temporal headache. His medical history was noteworthy for pulmonary embolism in 1982 and 1986, 3–4 packs/day cigarette smoking, and remote cocaine, amphetamine, marijuana, and alcohol abuse. Family history was remarkable for “blood clots” in both parents after age 60 years and “intestinal gangrene” in his father at age 72 years. Examination at the time of admission included normal vital signs, a normal cardiac examination, and no evidence of peripheral emboli, deep-vein thrombosis, or peripheral edema. He was inattentive and tangential and denied his neurologic deficits. He had dysarthric speech and a mild left hemiparesis, decreased sensation on the left, and a left homonymous inferior visual field defect.

Brain computed tomography and magnetic resonance imaging demonstrated recent infarction in the distribution of the right middle cerebral artery. Electrocardiogram, cardiac monitoring, and two-dimensional and contrast transthoracic echocardiograms were normal. Cerebral angiography demonstrated a smooth filling defect at the origin of the right internal carotid artery and occlusion of the right middle cerebral artery (Figure 2). Admission laboratory studies were normal except for a total serum protein concentration of 5.7 g/dl and an albumin content of 2.7 g/dl. Complete blood count, platelet count, prothrombin time, and partial thromboplastin time were normal. Erythrocyte sedimentation rate was 68 mm/hr. He had normal antithrombin-III, protein-S, protein-C, and plasminogen contents. Fibrinogen concentration was increased at 721 mg/dl. Free protein-S concentration was not obtained. Subsequent studies included urinalysis that demonstrated 2+ protein and 1+ blood and a 24-hour urine protein content of 6.6 g and a creatinine content of 2.9 (normal range 1–2) g. Assays for neutrophil cytoplasmic antibody, C3, C4, cryoglobulin, C-reactive protein, rheumatoid factor, and antinuclear antibodies, a hepatitis screen, and thyroid function studies were all normal or negative. Renal biopsy demonstrated membranous glomerulonephritis.

He was initially treated with subcutaneous heparin and later switched to aspirin 325 mg/day. He was not treated with long-term anticoagulation because of concerns about compliance and a high risk of complications related to his lifestyle. He received prednisone for his membranous glomerulonephritis. Four months after admission, he was readmitted with a pulmonary
Figure 2. Lateral and anteroposterior views of digital subtraction angiogram of case 2 showing smooth filling defect (arrow) of posterior wall at origin of right internal carotid artery (left) and occlusion of main trunk of middle cerebral artery, with collateral filling by anterior cerebral artery and its branches on delayed views (right).

embolus. The decision was then made to initiate full-dose anticoagulation with intravenous heparin followed by warfarin.

Discussion

Hypercoagulable states are recognized as factors in the development of arterial and venous thrombosis. Primary hypercoagulable states are usually congenital or familial and include deficiencies of antithrombin-III, protein-C, and protein-S, as well as other disorders of the coagulation or fibrinolytic systems. Secondary hypercoagulable states can be associated with a variety of underlying conditions including malignancy, pregnancy, and nephrotic syndrome.

Nephrotic syndrome has been associated with venous or arterial infarction of various organs. However, cerebral infarction has previously been reported in only three adults, and no report provides adequate information to exclude other mechanisms of infarction.

Both of our patients had isolated cerebral arterial distribution infarcts with no obvious underlying cause except for a hypercoagulable state related to nephrotic syndrome. Neither patient was known to have nephrotic syndrome before admission for his stroke. The mechanism by which nephrotic syndrome causes a hypercoagulable state is unclear, with theories including urinary loss of the body's own “anticoagulants” such as plasminogen, antithrombin-III, protein-C, and protein-S; increased hepatic production of clotting factors including fibrinogen; and increased platelet aggregability. Both of our patients were found to have an elevated fibrinogen concentration, which has been associated with an increased risk of stroke. However, fibrinogen can also be seen as a nonspecific acute-phase reactant. Even though levels of antithrombin-III, protein-C, and total protein-S were normal, one patient had a deficiency of the active, or free form of protein-S. This has been reported previously in patients with nephrotic syndrome. Our second patient was started on warfarin before a free protein-S level could be obtained.

Our patients represent two examples of cerebral infarction presumably due to a hypercoagulable state associated with nephrotic syndrome. Nephrotic syndrome should be considered as a contributing mechanism in any patient with ischemic stroke and pre-existing renal disease. In addition, ischemic stroke can be the presenting manifestation of nephrotic syndrome. In both patients, urinalysis was the initial clue to the diagnosis. This demonstrates the importance of this inexpensive and occasionally overlooked test in the evaluation of patients with acute stroke.

References


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Cerebral infarction in patients with nephrotic syndrome.
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