Cerebral Infarction in Young Men With Nephrotic Syndrome

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**Background and Purpose:** Thrombosis is one of the main complications of nephrotic syndrome; however, cerebral infarction associated with nephrotic syndrome has been rarely reported.

**Summary of Report:** We describe acute cerebral infarction in two young men with nephrotic syndrome. Both had a hypercoagulable state based on hemostatic studies. By retrospectively reviewing the medical records of the past 10 years at our hospital, we found an additional five cases of cerebral infarction with nephrotic syndrome. Two of the patients were found to have nephrotic syndrome during admission for stroke.

**Conclusions:** Hypercoagulability may be the major contributing factor of cerebral infarction in patients with nephrotic syndrome. (Stroke 1992;23:295-297)

Thrombotic phenomena are a well-recognized complication of nephrotic syndrome. Recent studies have shown the incidence of renal vein thrombosis to be 5-62% and that of pulmonary embolism 8%. Cerebral infarction associated with nephrotic syndrome has been rarely reported, however. The tendency of nephrotic patients to have thrombotic episodes has been attributed to a hypercoagulable state. We present two young male patients with acute cerebral infarction, probably due to a hypercoagulable state secondary to nephrotic syndrome. Retrospectively reviewing the medical records for the past 10 years, we found five more cases of nephrotic syndrome with cerebral infarction at our hospital.

**Case Reports**

**Case 1**

A 21-year-old man was admitted in January 1991 because of the sudden onset of weakness of the right limbs and headache. A diagnosis of nephrotic syndrome had been made in 1989, and he had received steroid therapy. Renal biopsy showed minimal change lesion. He had no history of hypertension or diabetes. He smoked half a pack of cigarettes a day for >3 years, but drank no alcohol and used no illicit drugs. On admission, he had a right hemiparesis, right homonymous hemianopsia, and decreased sensory perception on the right side. Cardiac examination was normal. He had no evidence of systemic embolization, peripheral edema, or deep-vein thrombosis.

Initial computed tomographic (CT) scan of the brain was normal, but a second scan 2 weeks later demonstrated a focal low-density area in the basal ganglia and internal capsule with marginal irregular enhancement. A cerebral digital subtraction arteriogram demonstrated occlusion of the left internal carotid artery just above the bifurcation with inadequate collateral circulation from the right side. The patient's chest roentgenogram, electrocardiogram, and transthoracic echocardiogram were normal. His blood count and electrolytes were within normal limits; however, blood urea nitrogen and creatinine levels were mildly elevated to 47 mg/dl and 1.6 mg/dl, respectively. Serum albumin concentration was 1.5 g/dl, cholesterol 683 mg/dl, and triglycerides 458 mg/dl. Urinalysis revealed 3+ protein. A 24-hour urine protein content was 5.62 g. Prothrombin time was normal. Activated partial thromboplastin time was increased 4 days after stroke, but returned to normal 10 days later. The 1:1 mixed activated partial thromboplastin time of patient and normal serum was normal. Thrombin time was mildly prolonged to 27 seconds (normal value <22 seconds). Fibrinogen concentration was normal. Antithrombin III level was 59% (normal 80-120%). The concentration of protein C was <12.5% (normal 70-140%). Assay of coagulation factors revealed the following values: factor V >100%, factor VII 30%, factor VIII >100%, factor IX >100%, factor XII 20%. Platelet aggregation tests were normal. The anticardiolipin antibody was negative.

The patient received antiplatelet therapy and gradually improved, but had a residual right hemiparesis at discharge 1 month later.

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Supported in part by grant CI-78-04 from Chin-Lin Medical Foundation.

Received August 7, 1991; accepted October 1, 1991.
Case 2

A 28-year-old man was admitted in January 1979 because of loss of consciousness, lasting for about 30 minutes, followed by incoherent speech. Nephrotic syndrome due to membranous glomerulonephritis proven by biopsy had been diagnosed 6 years previously, and he had been treated with steroids since then. In 1977, he developed occlusion of the abdominal aorta and had an endarterectomy with bypass graft from the abdominal aorta to both common femoral arteries. He smoked half a pack of cigarettes a day. He did not abuse alcohol or illicit drugs. There was no family history of stroke, heart disease, or other thrombotic disorders.

Examination of the patient on admission included normal vital signs and a normal cardiac examination, and there was no evidence of peripheral emboli, deep-vein thrombosis, or peripheral edema. He was awake, but sleepy at times. He had a mild right hemiparesis. Language examination showed partial impairment of fluency and comprehension, but with good repetition.

Brain CT scan demonstrated infarction in the distribution of left middle cerebral artery. Electrocardiogram showed an old anteroseptal myocardial infarction. M-mode and two-dimensional transthoracic echocardiograms demonstrated an aneurysm over the apical area with a 3-cm mural thrombus. Cerebral angiography demonstrated narrowing of the left A1 segment of the anterior carotid artery and the knee of the left middle cerebral artery.

Serum chemistry studies were normal except for a total serum protein concentration of 3.8 g/dl and an albumin concentration of 1.6 g/dl. Serum cholesterol level was 840 mg/dl and triglycerides 259 mg/dl. Total lipid content was 2,160 mg/dl (normal range 360-790). Blood count, prothrombin time, and activated partial thromboplastin time were normal. Erythrocyte sedimentation rate was 107 mm/hr. Antithrombin III level was 65% (normal 80-120%). The concentration of protein C was normal. Fibrinogen concentration was increased to 550 mg/dl. Antinuclear antibodies were negative, and C3 and C4 concentrations were normal. Urinalysis demonstrated 4+ protein, and 24-hour urine protein content was 7.85 g. The patient received anticoagulant therapy and had no further thromboembolic complications during 6 months of follow-up.

Apart from these two cases, we also retrospectively reviewed the medical records of patients with cerebral infarction and nephrotic syndrome at our hospital in the past 10 years. An additional five cases were found. Table 1 summarizes the characteristics, symptoms, and brain CT scans of all seven patients, including the two cases presented in this report. Four of the seven were <35 years of age. Unfortunately, complete hemostatic studies and cerebral angiograms were not performed in the earlier cases. In two cases, the diagnosis of nephrotic syndrome was made during admission for stroke, similar to diagnoses in the two cases reported by Marsh et al.5

Discussion

Thrombotic complications in patients with nephrotic syndrome occur in both venous and arterial systems. Whereas in adults the majority of thromboses are venous, arterial thromboses are more common in children. A hypercoagulable state is thought to be the major contributing factor.

Cerebral infarction in nephrotic syndrome is rare and has previously been reported in only six cases.3-7 Marsh et al5 described two adult patients, 34 and 36 years of age, who presented with acute cerebral infarction and were found to have a hypercoagulable state due to nephrotic syndrome. Both patients had increased fibrinogen concentration. One patient had a deficiency of free protein S, and the other had a pulmonary embolus 4 months after the stroke. Although it is not clear why nephrotic syndrome causes a hypercoagulable state, there have been many theories for its mechanism, such as urinary loss of antithrombin III,3 Factor XII deficiency,11 protein C and protein S deficiency,12 increased platelet aggre-
gation, and increased hepatic production clotting factors.

Our two patients had a hypercoagulable state. The first patient had protein C deficiency and decreased level of antithrombin III. Assay of his coagulation factors revealed depressed factors VII and XII and increased factors V, VIII, and IX. The second patient had a decreased level of antithrombin III and an increased concentration of fibrinogen. Because our first patient had a head injury 6 months before admission, one could argue that occlusion of the right ICA was attributable to traumatic dissection rather than in situ thrombosis. Doppler color flow imaging of the internal carotid artery only suggested carotid dissection. One could also argue that cerebral infarction of the second patient was caused by cardiac emboli from the mural thrombus rather than by middle cerebral artery thrombosis. However, the angiogram favors thrombosis rather than embolism. Because a hypercoagulable state was clearly demonstrated in both patients, we believe that this was the major contributing factor in their cerebral infarctions.

Some studies described an increased incidence of thrombotic complications and hypercoagulation during steroid treatment. Hypercholesterolemia may be another contributing factor in cerebral ischemia in nephrotic patients. Five patients in our series were treated with corticosteroids, and all but one in our series had elevated levels of cholesterol.

Ischemic strokes in young adults are uncommon and have different etiologies or risk factors from those in the elderly. While the majority are caused by cardiogenic emboli and premature atherosclerosis, a small number may be due to a hypercoagulable state secondary to nephrotic syndrome.

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Key Words: cerebral infarction • nephrotic syndrome • young adults
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Stroke. 1992;23:295-297
doi: 10.1161/01.STR.23.2.295

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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