Fulminant Cerebral Infarctions With Membranous Nephropathy

Seemant Chaturvedi, MD

Background: Arterial thromboses, including cerebral infarction, are a rare complication of the nephrotic syndrome.

Summary of Report: A 37-year-old woman presented with right upper extremity ischemia, left middle cerebral artery thrombosis, and right cerebellar infarction. She quickly herniated, and postmortem evaluation revealed membranous nephropathy. Increased fibrinogen and decreased free protein S levels were noted.

Conclusions: Membranous nephropathy can lead to rapidly progressive cerebral infarctions, with possible fatality. There is not a unifying hematologic explanation for the strokes seen with nephrotic syndrome. (Stroke 1993;24:473–475)

Key Words • cerebral infarction • nephrotic syndrome

The association between ischemic strokes in young adults and hypercoagulable states is well recognized. In a recent review, Hart and Kanter mention that more than a dozen primary hematologic disorders have been linked with ischemic stroke. One of the hypercoagulable states, the nephrotic syndrome, has been associated with both venous and arterial thromboses. Reports of cerebral infarction and nephrotic syndrome date back to 1969 and have been the subject of three recent detailed reports. Parag et al reported the case of a young man with minimal change disease and middle cerebral artery (MCA) thrombosis in 1990. In 1991, Marsh et al reported two instances of MCA occlusion in young men with nephrotic syndrome. Similarly, Fuh et al described two young men with underlying nephrotic syndrome who developed cerebral infarction while being treated with steroids, and they retrospectively identified five additional patients.

We describe a young woman with a fatal case of fulminant multifocal thromboses, including anterior and posterior circulations. Left hemispheric and right cerebellar infarction and membranous nephropathy were documented at autopsy. She differs from patients in the previously reported cases in that she had multifocal thromboses and a rapidly fatal clinical course as the initial manifestations of nephrotic syndrome.

Case Report

Our patient was a 37-year-old, mildly obese female who was admitted to another hospital with a 1-day history of nausea, vomiting, and change in mental status. Her medical history was significant for hypertension and preeclampsia during a prior pregnancy. The patient had smoked one-half to one pack of cigarettes daily for an unspecified length of time. Enalapril and atenolol had been prescribed for her in the past, but compliance was questionable.

Upon initial evaluation, the patient was afibrile, with a blood pressure of 180/110 mm Hg. She was disoriented but without obvious localizing neurological signs. Her right upper extremity was cool, pale, and without palpable pulses. A dampened radial pulse was obtained by Doppler.

After receiving a 5,000-unit bolus of intravenous heparin, the patient was transferred to our hospital. On admission, her blood pressure was 204/102 mm Hg. Her neurological exam was notable for an expressive aphasia and right hemiparesis. An ischemic right upper extremity was again noted.

Laboratory studies were notable for an erythrocyte sedimentation rate of 108 mm/hr. The prothrombin time was 11.9 seconds (normal, 10–13 seconds), partial thromboplastin time was 19.0 seconds (normal, 25–38 seconds), and platelet count was 754,000/mm³ (normal, 150–400/mm³). There was a decreased serum albumin concentration of 2.6 g/dL (normal, 4.0–6.5 g/dL) and a serum cholesterol level of 568 mg/dL. Her hematologic profile was notable for decreased free protein S of 45% (normal, 60–86%), normal total protein S, and an elevated fibrinogen level of 620 ng/dL (normal, 150–400 ng/dL). The antithrombin III level was 44 mg% (normal, 22–39 mg%), and protein C function was increased at 163% (normal, 70–133%). C4b binding protein was not measured. Anticardiolipin antibody, antinuclear antibody, and lupus anticoagulant were not detected. Urinalysis showed 3+ protein and an elevated specific gravity of 1.036. Electrocardiography showed normal sinus rhythm without evidence of previous myocardial infarction.

An arteriogram performed on admission revealed right axillary and radial artery thrombi, a small left
common carotid artery thrombus, and left MCA occlusion (Figure 1). Results from aortography and transesophageal echocardiography were normal. Cerebral infarction in the left MCA territory was demonstrated on a computed tomographic scan performed several hours later.

Intravenous heparin was started, and the patient was taken to the operating room, where she underwent thrombectomy of the right axillary and radial arteries. Within the first postoperative hour, reocclusion occurred, and a local urokinase infusion was begun. Later that day, she developed a right cerebellar infarction with brain stem compression and lapsed into a coma. A suboccipital craniotomy, with excision of infarcted tissue, was performed. Postoperatively, she developed a neurological picture of brain death, which was confirmed by a radionuclide scan.

Autopsy revealed concentric left ventricular hypertrophy as well as an old infarct in the posterior wall of the left ventricle. No vegetations, thrombi, or valvular pathology aside from aortic valve thickening were identified. The coronary arteries showed moderate atherosclerosis. A thrombus was identified in the descending aorta beyond the origin of the great vessels. Left cerebral and right cerebellar acute infarcts were seen, along with an occlusive thrombus in the left MCA. Diffuse cerebral edema was also present, with cerebellar tonsillar herniation. The kidneys showed early membranous nephropathy, with subepithelial intramembranous dense deposits present on electron microscopy. There was no evidence at autopsy of occult malignancy or a vasculitic process.

**Discussion**

Hypercoagulable states, reported to account for 7–17% of strokes in young adults,6,7 are traditionally classified as either primary or secondary.8 Primary hypercoagulable states are most often caused by deficiencies of physiological coagulation inhibitors and include antithrombin III deficiency, protein C deficiency, protein S deficiency, and fibrinolytic disorders.

The acquired hypercoagulable states include abnormalities of coagulation and fibrinolysis. These include such diverse conditions as malignancy, pregnancy, oral contraceptive use, the presence of a lupus anticoagulant, and nephrotic syndrome.

The most common manifestation of the hypercoagulable state associated with nephrotic syndrome is renal vein thrombosis, with an average incidence of 35%.9 This has been associated in particular with membranous glomerulonephritis, which was present in our patient. The incidence of thromboses at other sites averages 20%, with pulmonary embolism being the most frequent manifestation. The incidence of such thromboses is higher in adults than in children.10

Many coagulation abnormalities have been described in nephrotic syndrome. These include increased levels of factors V and VIII, increased fibrinogen levels, decreased plasminogen levels, deficiencies of antithrombin III/protein S, increased or decreased protein
C concentration, thrombocytosis, and enhanced platelet aggregability.  

As with the nephrotic syndrome in general, the reported cases of cerebral infarction and nephrotic syndrome have lacked a unifying hematologic factor. In both cases reported by Marsh et al.,4 the patients had increased fibrinogen levels, with normal antithrombin III; one also had a decreased level of free protein S. In both cases described by Fuh et al,5 the patients had decreased levels of antithrombin III, as did the patient of Parag et al.3 One patient of Fuh et al had a decreased protein C level as well.

Our patient displayed an elevated fibrinogen level. Because fibrinogen serves as a major determinant of plasma viscosity, this may have contributed in part to her thromboses. She also had reduced free protein S but normal total protein S, which would imply a reduced activity of protein S since the free fraction is the active fraction. The decrease in protein S is thought to be secondary to increased urinary losses, and this protein has been found in the urine of nephrotic patients.12

The patient outlined in the current report is the first young adult to be described with such malignant central nervous system hypercoagulability. She differs from earlier patients in that cerebral infarctions and systemic thromboses accompanied an initial presentation of membranous nephropathy, culminating in death 36 hours later; the patients of Marsh et al6 and Fuh et al5 were discharged in stable condition. Interestingly, most previously reported cases of cerebral infarction with nephrotic syndrome have occurred in males.

Upon initial presentation, our attention was directed to embolism from either a cardiac or aortic source. However, the ascending aorta was normal on angiography, and no definite cardioembolic source was found either antemortem or postmortem. Hart and Kanter1 have speculated that the transient abnormalities of coagulation inhibition and fibrinolysis associated with the nephrotic syndrome can precipitate thrombosis in synergy with underlying atherosclerosis. Our patient exemplifies this scenario in a particularly virulent form. She had evidence of cerebral and systemic thromboses that were refractory to local thrombolytics, conventional anticoagulation, and mechanical interventions. Her condition progressed over 24–36 hours to cerebellar herniation and brain death. Her clinical course was so rapid that a 24-hour urine collection was not feasible. However, she did manifest other characterisites of the nephrotic syndrome (proteinuria, hypoalbuminemia, and hypercholesterolemia) and had evidence of early membranous nephropathy.

We agree with others that urinalysis remains an important element in the assessment of the stroke patient and that careful evaluation for a prothrombotic disorder is warranted in young stroke patients. The present case serves as a reminder that the clinical and laboratory findings of nephrotic syndrome may signal the onset of a fulminant hypercoagulable state that can lead to infarctions in multiple vascular territories.

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References

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S Chaturvedi

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