Transient Ischemic Attack and Nephrotic Syndrome: Case Report and Review of Literature

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ABSTRACT: Thrombotic complications in patients with nephrotic syndrome are attributed to a hypercoagulable state. Venous thrombosis is common, but arterial thrombosis occurs less frequently in adult nephrotic patients. We report a case of recurrent transient ischemic attacks as an initial manifestation of nephrotic syndrome due to early-stage membranous glomerulonephritis, review the literature for similar cases, and briefly discuss this potentially life-threatening condition. We observed that transient ischemic attack or ischemic stroke could be the initial manifestation of nephrotic syndrome. Our observation may serve as reminder to consider nephrotic syndrome as a possible contributor when evaluating patients with transient ischemic attacks with no other discernable clues. A high index of suspicion alone avoids the unnecessary withholding of prophylaxis or treatment that can be life saving. **KEY INDEXING TERMS:** Nephrotic; Transient ischemic attack; TIA; Proteinuria. **[Am J Med Sci 2006;332(1):32–35.]**

Thrombosis is one of the main complications of nephrotic syndrome that has been attributed to a hypercoagulable state.[1,2] In certain settings, thromboembolic complications in nephrotic syndrome have significant morbidity and potential mortality. Appreciation of the pathophysiologic basis for organ dysfunction in nephrotic syndrome should lead to early recognition and treatment. In this article, we report a case of recurrent transient ischemic attacks (TIAs) as an initial manifestation of nephrotic syndrome, review the literature for similar cases, and briefly discuss this potentially life-threatening condition.

Case Report

A 61-year-old man presented with acute onset of left upper and lower extremity tingling and numbness that lasted for 2 minutes. Over the next month, he had two similar brief episodes. These episodes were not associated with any weakness, confusion, or difficulty in speaking. Carotid Doppler examination, echocardiography, and computed tomography of head yielded normal findings, and the patient was started on ticlopidine therapy. Over the next few weeks, he had recurrent symptoms, with as many as seven spells per day. The possibility of complex partial seizures was raised, and the patient was prescribed carbamazepine despite a normal electroencephalogram. There was no improvement in his symptoms and a subsequent magnetic resonance imaging scan of his brain was normal. Carbamazepine was discontinued and warfarin therapy was initiated for presumed recurrent cerebrovascular events. The patient's previous history indicated he had been taking a combination of atenolol and hydrochlorothiazide over the past 7 years for chronic stable hypertension, and there had been a recent change in regimen: enalapril was prescribed for worsening hypertension. A review of the patient's systems was remarkable for orthopnea and increased bilateral lower extremity swelling for the last 3 months. The patient was a nonsmoker and nonalcoholic and had no history of hepatitis, blood transfusion, retinopathy, neuropathy, HIV risk factors, underlying malignancy, or documented infectious disease. His blood pressure was 132/82 mm Hg and the physical examination was remarkable for 1+ edema of both lower extremities. Neurologic examination findings were unremarkable. His hemoglobin A1C was 5.7. Urinalysis showed 4+ protein, 1 to 2+ blood, 5 red cells per high-powered field, no red cell casts, occasional fat droplets, and rare hyaline casts and was negative for leukocytes, nitrite, ketone, and glucose. A 24-hour urine collection revealed total protein excretion of 3.9 grams. Urine protein electrophoresis was negative for Bence-Jones protein; hemoglobin was 13.9 g/dL, mean corpuscular volume was 64, creatinine concentration was 0.9 mg/dL, cholesterol level was 402 mg/dL, and albumin level was 2.5 g/dL. Renal ultrasonography showed normal renal size and normal cortex. Cardiac echography findings were normal. Hepatitis panel, antinuclear antibodies, and complement levels were all normal. Renal biopsy was performed. Light microscopy was normal, direct immunofluorescence studies were positive with anti-IgG and anti-C3 conjugates, and electron microscopy revealed abundant subepithelial electron-dense deposits with fusion of foot processes suggestive of early-stage membranous glomerulonephropathy. We saw the patient at this point, and other

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Submitted October 25, 2005; accepted in revised form April 7, 2006.

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than mild tingling involving the tips of his left hand, he had near total resolution of symptoms while taking warfarin (Coumadin).

Other Similar Previously Reported Cases

There have been several reports of cerebral infarction in adult patients with nephrotic syndrome, but TIA has been described only in a handful of pediatric patients,[3,4] as detailed in Table 1.

Discussion

Nephrotic syndrome may be associated with several complications caused by severe proteinuria. The consequences of severe renal protein loss include disturbance of water and electrolyte metabolism, thromboses and thromboembolic complications, and hyperlipidemia with accelerated atherosclerosis. In adult nephrotic patients, the majority of thromboses are venous, whereas arterial thromboses are more common in children.[5] In 2004, Yun et al[6] reviewed 12 cases of cerebral infarction in adults associated with nephrotic syndrome. The mean age was 38.1 yr (range, 21–59 yr). The underlying renal disease was membranous nephropathy in three patients, membranoproliferative glomerulonephropathy in three, minimal change disease in three, focal segmental glomerulosclerosis in one, IgA in one, and unknown in one. We reviewed TIA in patients with nephrotic syndrome published in English-language literature. Only three reported cases were found, all in association with nephrotic syndrome affecting children (Table 1). So far, there is no report of an adult patient presenting with symptoms of TIA. To our knowledge, this is the first case of an adult patient presenting with recurrent symptoms of TIA that was diagnosed early and started on anticoagulation to prevent a debilitating cerebral infarction.

A hypercoagulable state is thought to be the major contributing factor for thrombotic episodes associated with nephrotic syndrome. The mechanism by which nephrotic syndrome causes a hypercoagulable state is unclear. It is suggested that urinary loss of the body's own "anticoagulants" such as plasminogen, antithrombin III, protein-C, and protein-S may be contributing factors. Other possible mechanisms include increased platelet aggregability, increased viscosity of blood, defects in the fibrinolytic system, hemoconcentration, and administration of steroids and diuretics, as detailed below.

Altered coagulation cascade:

1. Increased levels of high molecular weight factors II, V, VII, X, and XIII.[5,7] Increase in the level of these factors correlates with hypoalbuminemia and represents increased synthesis of the factors.[5,8]

2. An increased level of fibrinogen is a consistent abnormality in nephrotic syndrome and has been shown to considerably alter the plasma viscosity.[1,5]

3. Increased levels of plasminogen activator.[5,9]

4. Increased levels of alpha-2-antiplasmin and alpha-2-macroglobulins.[5,7] Plasma plasminogen level is low in hypoalbuminemia and is directly proportional to the degree of proteinuria.[5,10]

5. Decrease in the concentration of low molecular weight coagulation factors XI and XII due to increased urinary losses because of their small molecular size.[5,8]

6. Decrease in antithrombin III (65,000 daltons), which is important in the inactivation of activated procoagulant factors, is reduced to less than 75% of the normal concentration, especially when the serum albumin concentration is less the 2 g/dL.[5,8]

7. Although levels of protein S and protein C are found to be increased in some studies and decreased in others, recently, deficiency of protein S has been implicated as a contributing factor to the thrombotic diathesis. (Protein C, a vitamin K dependent protein, inactivates the coagulation factors V and VIII. Protein S is a cofactor of activated protein C.)[5]

Platelet dysfunction:

1. Thrombocytosis, increased platelets aggregation and adhesiveness,[11] and an increase in the levels of the platelet release substance B-thromboglobulin[12,13] have been implicated in thrombotic complications.

2. Platelet hyperaggregability correlates well with degree of proteinuria as well as with plasma cholesterol levels, suggesting that urinary albumin losses or hyperlipidemia may play a role.

3. Platelet antiaggregatory activity of prostacyclin (PGI2) is well known. Serum albumin plays a major role in stabilization of this effect. The duration of this protection is proportional to the concentration of albumin.[14] It is also known that free fatty acids inhibit the synthesis of PGI2[15] and significantly diminishes the PGI2 protective effect of serum albumin by displacing PGI2 from binding sites on the albumin molecule.[16] Therefore, in nephrotic syndrome, where there is low albumin and high free fatty acids, PGI2 stability is substantially decreased, resulting in platelet hyperaggregability.[16]

Loss of vascular endothelial integrity:

1. Loss of functional integrity of endothelium as seen in nephrotic syndrome results in atherosclerosis.[5]

Increased blood viscosity:

1. Fahal et al. have suggested that increased blood viscosity leads to thromboembolic complications secondary to hemoconcentration, which is often exacerbated by diuretics.[5]

2. Blood viscosity in these patients is increased by increased plasma viscosity related to high fibrinogen concentration.[5,17,18]

Others:

1. Diuretics increase hemoconcentration and thus contribute to the thrombotic state.

2. Steroids alter the coagulation state by increasing several clotting factors and decreasing the fibrinolytic activity.[19] They raise factor VIII[20] and