CASE REPORT

Two Cases of Nephrotic Syndrome Presenting as Ischemic Stroke

Nephrotic syndrome may be more common than previously realized as a cause of hypercoagulability in ischemic stroke of unclear etiology.

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Nephrotic syndrome is a hypercoagulable state and an uncommon cause of ischemic stroke in young patients. It is easily missed, although a simple urinalysis can point a clinician to this etiology. We present two cases of young males with recurrent stroke in which extensive workup for stroke etiology was initially done, followed by workup for proteinuria to reveal a diagnosis of nephrotic syndrome.

Case 1

A 47-year-old male with a history of hypertension presented with acute right gaze deviation, left-sided hemiplegia, left hemineglect, and dysarthria. Computerized tomography (CT) showed hyperacute infarction in the right middle cerebral artery territory. He underwent emergent IV tissue plasminogen activator (tPA) treatment, followed by suction/stent retrieval, mechanical thrombectomy, and a hemicraniectomy. On admission, the patient was also noted to have left calf swelling as well as CT evidence of a previous (silent) stroke. Color and pulsed-Doppler imaging of his lower limbs confirmed deep vein thrombosis of the left peroneal and tibial veins. Echocardiogram results showed normal cardiac function and no patent foramen ovale by microbubble contrast.

The patient was noted to have a cholesterol level of 549mg/dL. Basic urinalysis revealed urine protein of greater than 1,000mg/dL, later confirmed at 464mg/dL (normal is less than 15 mg/dL). A 24-hour urine collection was 12,436mg/ 24 hours. His serum albumin level was 0.6gm/dL. Serum protein electrophoresis showed reduced total protein but increased α-1 and α-2 globulin, implying selective protein loss of renal origin-nephrotic syndrome. Renal biopsy showed PLA2R-negative stage 2 membranous glomerulonephritis.

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The patient started anticoagulation with warfarin (Coumadin, Bristol-Myers Squibb) one month after his craniotectomy and was prescribed cyclosporine for nephrotic syndrome. His left leg deep vein thrombosis continued to progress despite warfarin treatment, and he subsequently had vena cava filter placement and change in anticoagulation to rivaroxaban (Xarelto, Janssen).

He was re-admitted six months later for a cranioplasty, and his anticoagulation was temporarily suspended for surgery. Upon stopping his rivaroxaban, the patient developed a visual field defect, and an MRI scan confirmed a new occipital stroke.

Case 2

Our second patient is a 57-year-old male who was transferred to the rehabilitation facility at our hospital

to recover from a recent right thalamic stroke. He had significant risk factors for atherosclerosis, including diabetes, hypertension, hyperlipidemia, and current smoking. However, CT angiogram of the head and neck was clean, and he did not have cardiovascular disease elsewhere. The CT scan showed evidence of multiple previous strokes. MRI revealed an incidental further new punctate infarct in the left centrum semiovale.

This patient's recent hospital admission was notable for acute decline in his renal status and the initiation of hemodialysis. The cause of the renal failure was attributed to diabetes. His cholesterol level was 286mg/dL, urine protein was 450mg/dL, and his 24-hour urine protein test result was 11,910mg/24 hours. Albumin was 1.5gm/dL. His recent hospitalization was complicated by bilateral upper limb deep vein thrombosis, which was attributed to the placement of hemodialysis catheters. An embolic etiology of his multiple strokes was considered; however, a transesophageal echocardiogram and cardiac monitoring revealed no evidence of atrial fibrillation, cardiac thrombus, or patent foramen ovale. Considering the available information, it was determined that his multiple strokes were secondary to a hypercoagulable state, secondary to nephrotic syndrome, and he was started on warfarin treatment.

Discussion

Nephrotic syndrome is a hypercoagulable state and a rare cause of stroke in the young.[1] The mechanism of thromboembolism and optimal diagnostic and anticoagulant management strategies remain controversial. The underlying mechanisms of the "thrombophilia" of the nephrotic syndrome are multiple but seem to be related to an imbalance of prothrombotic factors (e.g., increased fibrinogen levels, increased factor VIII levels, increased platelet adhesiveness) and antithrombotic factors (e.g., reduced antithrombin III levels, reduced protein C and S levels or activity) and impaired thrombolytic activity (e.g., decreased plasminogen levels, elevated plasminogen activator inhibitor-1 levels, or albumin deficiency-related impairment of the interaction of plasminogen-fibrin).[2]

Subtle clues in the urinalysis and low serum albumin level may be missed. However, all stroke patients have their cholesterol checked, and if a marked hypercholesterolemia is detected, this condition should be considered.

We have had two recent cases of stroke associated with nephrotic syndrome in males under the age of 60 in the past six months at our community hospital. The patient in case 1 presented with large vessel occlusions, and the patient in case 2 had normal CT angiogram/magnetic resonance angiography results, with multiple smaller and relatively asymptomatic previous strokes. It is possible that nephrotic syndrome is more common than previously realized as a cause of hypercoagulability in ischemic stroke of unclear etiology.

Careful evaluation of routine tests can be most valuable. Urinary analysis will suggest nephrotic syndrome before the need to order more elaborate tests. Similarly, a complete blood count/peripheral blood smear will exclude many rare causes of hypercoagulable states and stroke in the young, such as anemia (e.g., paroxysmal nocturnal hemoglobinuria, Evans syndrome, vitamin B_{12} deficiency), platelet disorders (e.g., thrombotic thrombocytopenic purpura, thrombocythemia, heparin-induced thrombocytopenia and thrombosis), and myeloproliferative diseases, all of which have been associated with stroke.

Nevertheless, the role of the usual hypercoagulable workup (protein C/S deficiency, factor V Leiden mutation, prothrombin gene mutation, antiphospholipid syndrome, and antithrombin III) in patients with acute stroke has been questioned.[3,4] Protein C, S, and antithrombin III levels will be depressed in those with acute thrombosis, such as in the setting of a large middle cerebral artery stroke, and acute test results may be misleading.

Present guidelines on the routine anticoagulation of patients with nephrotic syndrome is unclear. A selective rather than a routine approach to prophylactic anticoagulation seems justified. A case can be made for prophylactic anticoagulation in patients with severe nephrotic syndrome (serum albumin concentration <2.0 to 2.5g/dL) as a result of membranous nephropathy when no contraindication to the use of long-term warfarin anticoagulation exists.[5] These cases suggest careful neurological evaluation for occult stroke in patients with nephrotic syndrome, as well as a lower threshold to start anticoagulation if there is evidence of nephrotic syndrome. Taking these steps may prevent more serious strokes in the future. ■

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