Embolic Stroke and Nephrotic Syndrome: A Case Report and Literature Review

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Abstract

Nephotic syndrome (NS) is less commonly associated with arterial thrombosis than venous thrombosis. We report a case of a 43-year-old woman who presented with an acute embolic stroke confirmed on MRI, about 3 months after the diagnosis of NS. The standard stroke evaluations did not show evidence of cardiac source of embolism, large vessel atherosclerosis or any primary hypercoagulable disorders. Laboratory tests revealed impaired renal function and extremely high nephrotic range proteinuria and a renal biopsy showed primary membranous glomerulonephropathy. Subsequently, she was discharged on anticoagulation and responded well to the treatment. This case illustrates the importance of considering hypercoagulable evaluation due to nephrotic syndrome as a potential cause of embolic stroke, and the initiation of anticoagulation therapy in a timely manner. We also present a literature review on the association between nephrotic syndrome and acute stroke.

Keywords: Stroke; Nephrotic syndrome; Hypercoagulable state; Arterial thrombosis

Introduction

It has been shown that patients with nephrotic syndrome (NS) are prone to thrombo-embolic phenomena [1, 2]. The risk of thrombo embolism is increased during the first 6 months of the onset of NS3. In adults with NS, arterial thrombo embolic events are not as well characterized and less commonly reported than venous thrombo embolism [4]. Acute ischemic stroke is a rare complication of NS [5,6,7] and this link has not been widely reported in the literature.

Although the exact pathogenesis of cerebral infarction is not clearly understood, it has been postulated that a hyper coagulable state in NS may play an important role in ischemic stroke [3,8]. Few studies have suggested that hyper coagulability in NS is associated with the steroid and diuretic administration [9]. Although there are case reports of NS and stroke [7,10-16], we report this case to illustrate the importance of considering hypercoagulability from NS as a potential cause of embolic stroke, and to initiate anticoagulation treatment if appropriate. Additionally, we performed an extensive literature search for NS and association with ischemic stroke.

Case Report

A 43-year-old, left-handed, woman presented with sudden onset of left sided weakness and word finding difficulty three months after the diagnosis of NS. Her other pertinent medical history included COPD, hypertension and was a smoker, with no significant family history for coagulation disorders. NS with membranous glomerulonephropathy was confirmed with biopsy during this admission. Medication history at the time of presentation included cyclophosphamide, prednisone, spironolactone, Lasix, Lisinopril and metoprolol. Her vitals were stable at presentation and general physical examination was benign. Her neurologic exam was significant for mild anoma and left sided weakness. Her laboratory tests showed impaired renal function and extremely high nephrotic range proteinuria and a renal biopsy showed primary membranous glomerulonephropathy. Subsequently, she was discharged on anticoagulation and responded well to the treatment. This case illustrates the importance of considering hypercoagulable evaluation due to nephrotic syndrome as a potential cause of embolic stroke, and the initiation of anticoagulation therapy in a timely manner. We also present a literature review on the association between nephrotic syndrome and acute stroke.

Table 1: Lab work up at the time of presentation.

| Test                        | Value       |
|-----------------------------|-------------|
| Total cholesterol           | 240mg/dl    |
| LDL                         | 164 mg/dl   |
| Triglycerides               | 314mg/dl    |
| HbA1C                       | 5.1 percent |
| Urine Specific gravity      | 1.008       |
| Spot urine protein          | >499mg/dl   |
| Factor V Leiden mutation    | Negative    |
| Prothrombin gene mutation   | Negative    |
| Anti-cardiolipin antibody   | Negative    |
| Protein C activity          | 113%        |
| Protein S activity          | 85%         |
Further work up included an MRI which revealed bihemispheric regions of diffusion restriction, consistent with acute infarcts (Figure 1). Her cardiac work up was essentially normal. Vascular imaging of the brain was obtained with a CT angiogram which showed a left MCA occlusion at the M3-M4 segments, without evidence of any proximal large artery atherosclerosis. Given the bihemispheric infarcts, an underlying embolic source was likely. After an exhaustive cardiac work up did not reveal any source of cardio embolism, the possibility of hypercoagulability with significant proteinuria due to NS was considered the likely etiology, and anticoagulation was initiated.

## Literature Review

Systematic searches of peer-reviewed, published, research papers indexed in PubMed, EMBASE, and Science Direct from inception until Nov. 2016 were undertaken using key search terms related to ‘Nephrotic Syndrome’, ‘ischemic stroke’, and ‘infarction’. We identified 30 reported cases of acute ischemic strokes with NS after eliminating 10 cases with nephropathy related to DM. The age at the presentation ranged from 14 -73 years with a mean age of 40.7, and standard deviation 15.7 years. 70% of the cases (21/30) were male. Among 30 there were only 5 cases without a biopsy-proven diagnosis of NS, most of the cases (8/30) were membranous disease. The other cases were associated with Membrano proliferative Glomerulo nephritis, minimal change disease, IgA nephropathy, IgM nephropathy, Focal Segmental Glomerulo sclerosis and nodular glomerulopathy (Table 2). These infarcts have been described in various vascular distributions.

### Table 2: Literature review of nephrotic syndrome and stroke.

| S No | Age | Sex | Territory of stroke | Risk factors | Renal disease and duration | Treatment given | Abnormal Lab Data | Reference | Year |
|------|-----|-----|---------------------|--------------|---------------------------|----------------|------------------|-----------|------|
| 1    | 52  | M   | L. corona radiata   | Unknown      | Unknown                   | Unknown        | Unknown          | Miyamoto T et al | 1989 |
| 2    | 23  | M   | L-MCA               | Alcohol intake, Postmortem diagnosis | Minimal change disease, Postmortem diagnosis | furosemide, albumin, cephamandole, and heparin | Albumin(0.7 g/dL) ↓ fibrinogen (1440 mg/dL) ↑↑↑ Factor VIII (150 to 400 mg/dL) ↑↑↑ antithrombin III (36%) ↓ protein C activity (66%) ↓ 24hr urine protein( 10g) ↑↑↑ | Parag KB et al | 1990 |
| 3    | 23  | M   | R MCA               | Unknown      | unknown                   | unknown        | unknown          | Sekiguchi et al | 1990 |
| 4    | 34  | M   | R ICA               | Smoking, H/o PE x 2 , family H/O of clotting disorders, cocaine, amphetamine use | Membranous glomerulonephritis. New diagnosis. | Steroid, heparin, warfarin and aspirin. | Total protein (5.7 g/dL) ↓ Albumin(2.7 g/dL) ↓ Fibrinogen (721mg/dl) ↑↑ ↑↑ 24hr urine protein( 6.6g) ↑↑↑ | Marsh et al | 1991 |
| No. | Age | Gender | Side | Type | Diagnosis | Treatment | Clinical Findings | Reference |
|-----|------|--------|------|------|-----------|-----------|------------------|-----------|
| 5   | 36   | M      | L-MCA | NA   | Membrano proliferative glomerulonephritis. | Heparin and warfarin. | Total protein (4.1 g/dL) ↓ Albumin (2.4 g/dL) ↓ Protein S activity (55%) ↓ Fibrinogen (701 mg/dL) ↑↑ Plasminogen conc (145%) ↑↑ 24hr urine protein (1.4g) ↑↑↑ | Marsh et al 1991 |
| 6   | 51   | M      | R MCA | Smoking | Unknown type of nephrotic syndrome. New diagnosis. | Unknown | Total protein (4 g/dL) ↓ Albumin (2 g/dL) ↓ Fibrinogen (692 mg/dL) ↑↑ Plasminogen conc (66%) ↓ Antithrombin III Activity (69%) ↓ Total cholesterol 405 mg/dL ↑↑ | Fritz et al 1992 |
| 7   | 28   | M      | L-MCA | Smoking | Membrano Nephropathy for 6 yrs. | Steroid | Total protein (3.8 g/dL) ↓ Albumin (1.6 g/dL) ↓ Fibrinogen (550 mg/dL) ↑↑ Antithrombin III Activity (65%) ↓ 24hr urine protein (7.85 g) ↑↑↑ Total cholesterol 840 mg/dL ↑↑ | Fuh et al 1992 |
| 8   | 21   | M      | L-ICA | Smoking | Minimal change lesion. 2 years after diagnosis. | Antiplatelet therapy | Albumin (1.5 g/dL) ↓ Antithrombin III Activity (59%) ↓ protein C activity (12.5%) ↓ 24 hr Urine protein 5.62 gm ↑↑ Total cholesterol 683 mg/dL ↑↑ | Fuh et al 1992 |
| Case # | Age (y) | Gender | Location | Associated Conditions | Lab Findings | Treatment | Reference |
|--------|---------|--------|----------|----------------------|-------------|-----------|-----------|
| 9      | 30      | M      | Basilar artery | Mild HTN, Smoking, hyperlipidemia, membranoproliferative glomerulonephritis. 10 months earlier | Total protein (5.1 g/dL) ↓, Albumin (2.9g/dL) ↓, Total cholesterol 857mg/dl ↑ | Unknown | Leno et al 1992 |
| 10     | 37      | M      | L-MCA    | HTN and smoking | Membranous Nephropathy diagnosed at autopsy, Iv heparin | Albumin (2.9g/dL) ↓, Fibrinogen (620mg/dl) ↑↑, Protein C activity (45%) ↓, Antithrombin III Activity (44%) ↓, Total cholesterol 568mg/dl ↑ | Chauturvedi et al 1993 |
| 11     | 39      | M      | R-frontal lobe | Unknown | Membranous proliferative glomerulonephritis diagnosed 2 yrs prior | Total protein (3.8g/dL) ↓, Albumin (2.0g/dL) ↓, Free protein S antigen (40%) ↓, Total cholesterol 235mg/dl ↑ | Song et al 1994 |
| 12     | 29      | F      | R-ICA    | Mild HTN and HLD | Membranous proliferative glomerulonephritis. Diagnosed 15years back, Prednisone and warfarin | Total protein (5.8g/dL) ↓, Albumin (3.8g/dL) ↓, 24 hr Urine protein 2.2 gm ↑, Fibrinogen (617mg/dl) ↑, Factor VIII (282%) and IX (162%) ↑↑, Total cholesterol 290mg/dl ↑ | Maruyama et al 1995 |
| 13     | 45      | M      | PCA      | Unknown | Membranous glomerulonephritis. New diagnosis. | Albumin (2.6g/dL) ↓, 24 hr Urine protein > 3.5gm ↑↑, Fibrinogen (1249 mg/dl) ↑↑ | De guana et al 1996 |
| 14     | 28      | F      | R-MCA    | Smoking and DM | Unknown (Patient refused biopsy). Edema since 1 month, Steroid, ACEI, Aspirin | Albumin [2.6g/dL] ↓, 24 hr Urine protein > 3.5gm ↑↑, Total cholesterol 294mg/dl ↑ | Kotani et al 1997 |
| 15     | 19      | F      | R-ICA    | Unknown | FSGS for 16yrs | Steroid | Unknown | Izumi et al 1998 |
| 16     | 59      | M      | B/L- Occipital | NA | Membranous Nephropathy. New diagnosis, Steroid, albumin, lasix | Albumin [1.7g/dL] ↓, Fibrinogen (680mg/dl) ↑↑, Antithrombin III Activity (65%) ↓, 24 hr Urine protein 12gm ↑↑ | Ogawa et al 1999 |
| Case Number | Age | Gender | Region | Diagnosis | Duration | Treatment | Laboratory Values | Reference |
|-------------|------|--------|--------|-----------|----------|------------|-------------------|-----------|
| 17          | 42   | F      | R-ACA, MCA | HTN and smoking | Minimal change disease. Diagnosed 11 years ago. | Steroid | Total protein (4g/dL) ↓ | Pandian et al 2000 |
| 18          | 35   | F      | L-temporal and parietal area | NA | IgA Nephropathy. 5 Years since diagnosis. | Steroid, Lasix, heparin, albumin infusion, thrombectomy | Total protein (4.4g/dL) ↓ | Lee et al 2000 |
| 19          | 47   | M      | L MCA | HTN, DM | Unknown | unknown | Hypoproteinemias. | Naganuma et al 2003 |
| 20          | 53   | M      | R-MCA | Smoking, cirrhosis | FSGS. 3 weeks | Steroid, ACEI, Diuretics, | Total protein (3.3g/dL) ↓ | Yun et al 2004 |
| 21          | 34   | M      | ICA occlusion | Unknown | Unknown duration | Steroid, aacenocumarol. | 24 hr Urine protein 12gm↑ | Navascués et al 2006 |
| 22          | 42   | M      | L ICA | Smoking | IgM nephropathy. For 6 years | Steroid, enalapril and diuretic | Albumin (1.4g/dL) ↓ Total cholesterol 390mg/dl↑ | Wiroteurairueng et al 2007 |
| 23          | 73   | F      | L- MCA | NA | Nodular Glomerulopathy diagnosed 2 months ago. | Steroid, albumin infusion, Lasix and spironolactone. | Albumin (1.8g/dL) ↓ Total cholesterol 556mg/dl↑ | Shib-MengYeh et al 2010 |
| 24          | 14   | F      | R-MCA | NA | Minimal change disease | Mizoribine, Steroid | Heavy proteinuria and serum albumin of 0.9mg/dl | Sugimoto et al 2012 |
| 25          | 68   | M      | R MCA and R PCA | HTN | Minimal change disease. Diagnosis at presentation | Steroid | Albumin (1.6g/dL) ↓ 24 hr Urine protein 14gm↑ | Babu et al 2013 |
| 26          | 71   | M      | B/L periventricular | HTN | membranous glomerulonephritis. Diagnosed at the time of presentation. | Steroid, statin, cyclosporine, ACE inhibitors, anticoagulants | Total protein (5.1 g/dL) ↓ Albumin (2g/dL) ↓ Fibrinogen (660mg/dl) ↑ Antithrombin III Activity (59%) ↓ Free protein S (56%) ↓ 24 hr Urine protein 21gm ↑ | Babu et al 2013 |
Discussion

In this case of acute embolic stroke in the setting of NS (primary membranous glomerulopathy) with a normal coagulation profile, the initial differential diagnoses for the etiology of the embolic infarcts were cardioembolism, atheroembolism and a primary hypercoagulable state. The work up for these, as outlined in the case were negative. Our standard hypercoagulable panel was normal in this case, but this maybe confounded by the concomitant use of steroids. Other clotting factors that are not included in the standard hypercoagulable panel may be affected due to large amounts of urinary protein loss [17]. Marsh et al reported a similar case of stroke in NS with normal coagulation profile except for activated free protein S level [5]. As Fibrinogen is an acute phase reactant and has been associated with elevations in acute stroke with uncertain prognostic value, the fibrinogen level was not checked in our case. [18,19] Increased fibrinogen levels after vascular event is associated with recurrence of stroke and MI [20]. As the likelihood of hypercoagulability secondary to NS was high on the differential, she was discharged on anticoagulation and high intensity statin. She has remained stable since then, with no further vascular events.

Thrombosis is a major complication of NS. Although both arterial and venous thromboses occur, arterial thrombosis is rare and has been described in the femoral arteries commonly [7], but not in cerebral vasculature. Venous thrombosis is more common in the adult patient population while arterial thrombosis is more common in the pediatric patient population [4]. Primary hypercoagulable states like congenital or hereditary deficiencies of protein C, protein S and antithrombin-III are relatively rare inherited conditions that lead to endothelial dysfunction [21].

Secondary hypercoagulable states can be associated with underlying conditions such as pregnancy, malignancy, NS or oral contraceptive use [21]. Hypercoagulable states result from the imbalance between the pro-coagulant and anticoagulant factors. The primary glomerular defect in NS results in leakage of high amount of high molecular weight protein, which consist many hemostatic regulatory proteins [22,23]. The overall hypoproteinemia is compensated by increased hepatic synthesis of high molecular weight clotting factors V, VII, VIII and X [24,25]. Increased urinary excretion of natural anticoagulant protein S, anti-thrombin III [26,27] has been reported.

Taken together, then the hemostatic balance is shifted towards a pro-coagulable state. As steroids may increase the concentration of anti-thrombin III and factor VIII [10], the levels of these clotting factors can be normal in NS patients taking steroids. Furthermore, diuretics can also lead to hypercoagulability due to hypovolemia and hemoconcentration. NS is also associated with thrombocytosis and platelet hyperaggregability [25]. In addition, immunologically mediated glomerular damage triggers extrinsic coagulation pathway and thus hypercoagulability [28]. Our review of current literature suggests that most of the acute stroke cases in NS are amongst young, predominantly male patients, and have relatively fewer other vascular risk factors. Hypercoaguable panels were not consistently abnormal, which is indicative of the limitations of current standard laboratory testing for this type of patients.

Conclusion

In patients with cryptogenic ischemic stroke with concomitant nephrotic syndrome, anticoagulation for the secondary prevention of stroke and other thromb-embolic events should be considered. Future prospective or randomized trials are needed to evaluate the link between NS and acute stroke as well as efficacy of anticoagulation therapy.

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