Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: https://www.tandfonline.com/loi/irnf20

Cerebral Sinovenous Thrombosis Associated with Factor V Leiden and Methylenetetrahydrofolate Reductase A1298C Mutation in Adult Membranous Glomerulonephritis

Sultan Ozkurt, Gokhan Temiz, Suzan Saylisoy & Mehmet Soydan

To cite this article: Sultan Ozkurt, Gokhan Temiz, Suzan Saylisoy & Mehmet Soydan (2011) Cerebral Sinovenous Thrombosis Associated with Factor V Leiden and Methylenetetrahydrofolate Reductase A1298C Mutation in Adult Membranous Glomerulonephritis, Renal Failure, 33:5, 524-527, DOI: 10.3109/0886022X.2011.573892

To link to this article: https://doi.org/10.3109/0886022X.2011.573892

Published online: 18 Apr 2011.

Submit your article to this journal

Article views: 276

View related articles

Citing articles: 2 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=irnf20

Renal Failure, 33(5): 524–527, (2011)
Copyright © Informa Healthcare USA, Inc.
ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2011.573892

informa
healthcare

CASE REPORT

Cerebral Sinovenous Thrombosis Associated with Factor V Leiden and Methylenetetrahydrofolate Reductase A1298C Mutation in Adult Membranous Glomerulonephritis

Sultan Ozkurt[1], Gokhan Temiz[1], Suzan Saylisoy[2] and Mehmet Soydan[1]

[1]*Department of Nephrology, Faculty of Medicine, Eskisehir Osmangazi University (ESOGU), Meselik, Eskisehir, Turkey;*
[2]*Department of Radiology, Faculty of Medicine, Eskisehir Osmangazi University (ESOGU), Meselik, Eskisehir, Turkey*

Abstract

Thromboembolic diseases are accepted as the most important complications in adult nephrotic syndrome, particularly membranous nephropathy. As renal vein thrombosis is usually seen in patients with membranous nephropathy, cerebral venous thrombosis is a very rare condition, which has not been reported previously in adult patients with membranous nephropathy. Although acquired dysfunctions of coagulation and fibrinolytic systems are responsible for hypercoagulopathy in patients with nephrotic syndrome, the two most common causes of hereditary venous thrombosis [the mutations of factor V Leiden and methylenetetrahydrofolate reductase (MTHFR)] facilitate thrombosis in arterial and venous system in these patients. We report a 56-year-old man with sinovenous thrombosis, diagnosed as membranous nephropathy and detected to have mutations in factor V Leiden and MTHFR A1298C. Our patient is important because he had genetic risk of thrombotic conditions and was the first adult patient with membranous nephropathy.

Keywords: Thromboembolic disease, membranous nephropathy, cerebral venous thrombosis, MTHFR A1298C, mutation

Copyright © 2011 Informa Healthcare
Not for Sale or Commercial Distribution
Individual use only
Unauthorised use prohibited. Author's personal use only.
You may view and print a single copy for personal use.

INTRODUCTION

The most common clinical finding of nephrotic syndrome is generalized edema. Patients with nephrotic syndrome are at an increased risk of bacterial infections, electrolyte abnormalities, and venous thrombosis.[1] Renal vein thrombosis is a well-recognized complication in patients with nephrotic syndrome, especially membranous nephropathy, and its incidence ranges between 5% and 62% (mean 35%). There are potential mechanisms such as loss of anticoagulants [i.e., antithrombin III (AT III)] in urine, increase in fibrinogen levels, platelet activity and synthesis of procoagulant proteins, thrombocytosis, and changes in fibrinolytic system with a tendency to hypercoagulation.[2] The use of diuretic drugs and subsequent volume contractions contribute to the development of thrombosis in patients with nephrotic syndrome.[1] However, other potential causes of hypercoagulopathy such as hereditary thrombophilia are not well documented.[3] As factor V Leiden mutation is the most common cause of hereditary venous thrombosis, methylenetetrahydrofolate reductase (MTHFR) mutation is responsible for hereditary hyperhomocysteinemia and is a genetic risk factor to vascular diseases.[4] Although adult membranous nephropathy is especially associated with renal venous thrombosis,[5,6] there is no previous report of sinovenous thrombosis (SVT) in adult patients with membranous nephropathy. We report the case of a 56-year-old man with idiopathic membranous nephropathy associated with SVT due to factor V Leiden and MTHFR A1298C mutations.

CASE REPORT

A 56-year-old man was referred to our hospital because of proteinuria detected in another medicine department (complaint of swelling on face and bilateral

Address correspondence to Gokhan Temiz, Department of Nephrology, Faculty of Medicine, Eskisehir Osmangazi University (ESOGU), Meselik, 26140 Eskisehir, Turkey. Tel.: +90 222 2392979-2300; Fax: +90 222 2293489; E-mail: gokhan_tem@hotmail.com

Received 28 November 2010; Revised 24 February 2011; Accepted 14 March 2011

legs). There was no history of systemic illness or use of medicine. On physical examination, there was no pathologic finding except for edema in the legs. Laboratory examination revealed protein in the urine (+4), hemoglobin level of 15.2 g/dL, white blood cell count of 5170/mm^3, and platelet count of 279.000/mm^3. Erythrocyte sedimentation rate was 60 mm/h. Blood urea nitrogen, creatinine, glucose, electrolytes, prothrombin, and partial thrombin time were normal; 24 h urine protein was 12 g. The results of biochemical tests were as follows: total protein 4.8 g/dL, albumin 2.5 g/dL, total cholesterol 405 mg/dL, complement C3 236 mg/dL (79–152 mg/dL), complement C4 33.7 mg/dL (16–38 mg/dL), fibrinogen 423 mg/dL (180–400). Antinuclear, anti-double-stranded DNA, antiphospholipid, anticardiolipin, hepatitis C, human immunodeficiency virus antibodies, and hepatitis B antigen were negative. Serum protein electrophoresis and chest radiography were normal. Fecal occult blood was negative. In renal biopsy result, there were 14 glomeruli, 2 of which showed thickening of basal membrane, 2 of which were glomerular sclerosis, and remaining 10 showed thickening of glomerular capillary without hypercellularity. Immunofluorescence exam with IgG and C3c revealed markedly granular deposits on glomerular capillary wall, and IgA, IgM, C1q, and fibrinogen were negative. Electron microscope imaging could not be performed. As a result, all of these findings were consistent with membranous nephropathy. Because of the sudden headache and convulsion developed 3 days after biopsy, cranial computed tomography (CT) was performed. On CT exam, acute thrombus in right transverse and straight sinuses, and subarachnoid hemorrhage in left frontal region were detected (Figure 1). Thrombophilia screening tests were as follows: AT III activity 27 mg/dL (25–36), protein C 118% (60–130), and protein S 98.8% (55–140). Genetic evaluation revealed no mutation in prothrombin gene, heterozygote mutation in factor V Leiden, and homozygote mutation in MTHFR A1298C gene. Homocysteine level was found to be 16.5 μmol/L.[4–14] Unfractionated heparin followed by warfarin was immediately begun and then the dose was regulated according to coagulation situation. In the first, third, and fifth months of treatment, intravenous pulse methylprednisolone at 1 g/dose on the first 3 days and daily oral methylprednisolone at 0.5 mg/kg on the remaining days were given. In addition, the patient also received oral cyclophosphamide at 2.0–2.5 mg/kg/day for the second, fourth, and sixth months. An angiotensin II receptor blocker (irbesartan 300 mg, once a day) was initiated at the same time with immunosuppressive therapy.

The patient was discharged after recovery from the thrombotic condition. At the second month of treatment, the proteinuria decreased at 3 g/24 h, albumin increased at 3 g/dL, and renal functions were stable. A control nonenhanced axial CT image was performed 7 months after diagnosis. Compared to previous findings, regression of right transverse sinus thrombosis was observed. The subarachnoid hemorrhage and cerebral edema were resolved (Figure 2).

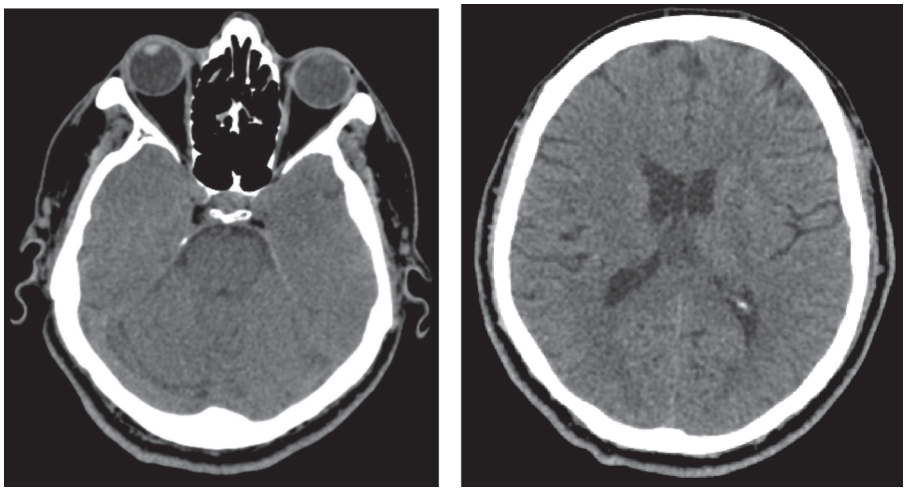
DISCUSSION

Adult patients with nephrotic syndrome have increased risk of thrombosis in arterial and venous systems when compared with children with nephrotic syndrome.[1] Although renal vein thrombosis is a common complication in patients with nephrotic syndrome,[1] SVT is not a common condition. To date, minimal change disease constitutes the majority of a few reports of adult nephrotic syndrome associated with SVT,[7–10] and SVT concomitant with membranous nephropathy has not been previously reported.



Figure 1. (A) Nonenhanced axial CT image shows high density in the right transverse sinus, suggesting acute thrombosis and loss of grey–white matter differentiation throughout the cerebral hemispheres, consistent with diffuse edema. (B) The straight sinus is seen hyperdense due to the presence of thrombus on sagittal reformatted CT image. (C) Nonenhanced CT image passing lateral ventricle level shows localized subarachnoid hemorrhage in left frontal region.

© 2011 Informa Healthcare USA, Inc.



(A) (B)

Figure 2. (A) Nonenhanced axial CT scan obtained 7 months later exhibits recovery of high density in the right transverse sinus. (B) The CT scan passing through lateral ventricle shows that the subarachnoid hemorrhage at the left frontal region and cerebral edema are resolved.

There is a tendency to hemostatic system activation and thrombosis in nephrotic syndrome. The changes of coagulant factors, defect of fibrinolytic activity, and platelet dysfunctions contribute to this condition.[6] Abnormality in coagulation system is caused by increased production of coagulation factors by the liver, loss of AT III and plasminogen in urine, and accelerated thrombin generations.[6–11] Nephrotic syndrome may be associated with acquired hypercoagulability. However, if this condition accompanies an underlying hereditary thrombophilia, thrombotic processes can occur. Hereditary tendency to venous thrombosis rarely causes spontaneous thrombotic condition prior to puberty.[12] Genetic aspects of thrombotic disease in adult patients with nephrotic syndrome are not well investigated and are reported as case reports.[13]

Factor V Leiden mutation is the most common cause of hereditary thrombophilia and constitutes 40–50% of all cases. There are guanine to adenine substitution at nucleotide position 1691 of the factor V gene and a substitution of arginine to glutamine at position 506 on the molecular basis of resistance to activated protein C. Heterozygote mutation of factor V Leiden is responsible for 90–95% cases of Activated Protein C (APC) resistance. The risk of thromboembolism increases 7 times with heterozygote mutations of factor V Leiden and 80 times with homozygote mutations.[14] Previous studies indicated that patients with nephrotic syndrome who had factor V Leiden mutation had high risk for thromboembolic conditions.[2] There is an increased risk for cerebral vein thrombosis in factor V Leiden mutation, and cerebral venous thrombosis is seen in patients with factor V Leiden mutation five or six times more than in control group.[15] There was one child who had factor V Leiden mutation with arterial thrombosis in literature but there was no reported case of SVT with membranous nephropathy.[16]

The two most common polymorphisms in MTHFR gene (C677T and A1298C) cause reduction of enzyme activity, leading to increased level of homocysteine which is a risk factor for cerebrovascular and cardiovascular disease. The MTHFR enzyme activity was reduced by 60% in patients with homozygote and 30% in patients with heterozygote for C677T polymorphism, and 35–45% in patients with homozygote and 10% in patients with heterozygote for A1298C polymorphism. Thus, both polymorphisms can cause reduction of enzyme activity and consequently result in increased homocysteine level.[17] Homocysteine level in our patient was a little higher than normal.

The risk of thrombosis in nephrotic syndrome is closely related to the severity of disease (proteinuria >10 g/day), especially low levels of albumin (<2 g/dL).[18] Our patient had severe proteinuria but albumin level was not less than 2 g/dL. However, he had both heterozygote mutation for factor V Leiden and homozygote mutation for MTHFR A1298C. We think that the presence of these mutations facilitates the thrombosis in atypical locations. There are many causes of hypercoagulability in nephrotic syndrome. When ordinary causes have failed to explain thrombotic condition, hereditary thrombotic risk factors, particularly factor V Leiden mutation, have to be investigated because of the heterozygote mutation for factor V Leiden leading to the risk for SVT, especially in the early period of the disease. In addition, immunosuppressive treatment has to be begun immediately in order to preserve renal function and reduce exposing time to nephrotic syndrome for minimizing the risk of thromboembolic complication.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Louis CU, Morgenstern BZ, Butani L. Thrombotic complications in childhood-onset idiopathic membranous nephropathy. *Pediatr Nephrol.* 2003;18:1298–1300.

[2] Llach F. Hypercoagulability, renal vein thrombosis and other thrombotic complications of nephrotic syndrome. *Kidney Int.* 1985;28:429–439.

[3] Schlegel N. Thromboembolic risks and complications in nephrotic children. *Semin Thromb Hemost.* 1997;23:271–280.

[4] Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med.* 1994;8:517–522.

[5] Cameron JS. Coagulation and thromboembolic complications in the nephrotic syndrome. *Adv Nephrol.* 1984;13:75–114.

[6] Sagripanti A, Barsotti G. Hypercoagulability, intraglomerular coagulation, and thromboembolism in nephrotic syndrome. *Nephron.* 1995;70:271–281.

[7] Komaba H, Kadoguchi H, Igaki N, Goto T. Early detection and successful treatment of cerebral venous thrombosis associated with minimal change nephrotic syndrome. *Clin Nephrol.* 2007;68:179–181.

[8] Hirata M, Kuroda M, Koni I. Cerebral venous thrombosis in minimal change nephrotic syndrome. *Nippon Jinzo Gakkai Shi.* 1999;41:464–468.

[9] Urch C, Pusey CD. Sagittal sinus thrombosis in adult minimal change nephrotic syndrome. *Clin Nephrol.* 1996;45:131–132.

[10] Burns A, Wilson E, Harber M, Brunton C, Sweny P. Cerebral venous sinus thrombosis in minimal change nephrotic syndrome. *Nephrol Dial Transplant.* 1995;10:30–34.

[11] Lau SO, Tkachuck JY, Hasegawa DK, Edson JR. Plasminogen and antithrombin III deficiencies in the childhood nephrotic syndrome associated with plasminogenuria and antithrombinuria. *J Pediatr.* 1980;96:390–392.

[12] Fabri D, Belangero VMS, Annichino-Bizzacchi JM, Arruda VR. Inherited risk factors for thrombofilia in children with nephrotic syndrome. *Eur J Pediatr.* 1998;157:939–942.

[13] Kahveci SN, Seyahi E, Altıparmak MR, Ataman R, Serdengeçti K. Homozygous factor V Leiden mutation and disseminated thrombosis in a patient with nephrotic syndrome. *J Nephrol.* 2007;20:103–106.

[14] Atahan E, Çağlar E, Şarkış C, Uğurlu S. Venous thromboembolism and inherited thrombophilia. *Turkish J Thorac Cardiovasc Surg.* 2009;17:302–311.

[15] Juul K, Tybjaerg-Hansen A, Steffensen R, Kofoed S, Jensen G, Nordestgaard BG. Factor V Leiden: The Copenhagen City Heart Study and 2 meta-analyses. *Blood.* 2002;100: 3–10.

[16] Büyükçelik M, Karakök M, Başpınar O, Balat A. Arterial thrombosis associated with factor V Leiden and methylenetetrahydrofolate reductase C677T mutation in childhood membranous glomerulonephritis. *Pediatr Nephrol.* 2008;23:491–494.

[17] Weisberg I, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. *Mol Genet Metab.* 1998;64:169–172.

[18] Dahlback B. İnherited thrombophilia: Resistance to activated protein C as a pathogenetic factor of venous thromboembolism. *Blood.* 1995;85:607–614.

© 2011 Informa Healthcare USA, Inc.