Ischemic stroke in anti-phospholipase A2 receptor antibody-positive primary membranous nephropathy: clinical and neuroimaging characteristics

Jing Zhang, Jun-Long Shu, Qian You, Wei Zhang, Yi-Ning Huang

Department of Neurology, Peking University First Hospital, Peking University, Beijing 100034, China.

Primary membranous nephropathy (PMN) is the most common cause of nephrotic syndrome in adults. Most patients with PMN have circulating immunoglobulin G4 autoantibody to the podocyte membrane antigen phospholipase A2 receptor (PLA2R). Venous thromboembolism is a common and important complication of nephrotic syndrome, while arterial thromboembolic events such as coronary, peripheral, and cerebral infarctions are rarely seen. Ischemic stroke (IS) in patients with nephrotic syndrome has been described in several reports. But the etiology of IS, the correlation between IS and kidney disease or anti-PLA2R antibodies, the prognosis of IS, and the imaging characteristics in such patients have not been fully elucidated. In the present study, we reviewed the clinical and neuroimaging characteristics of patients with IS and anti-PLA2R antibody-positive PMN to identify the correlation between IS and anti-PLA2R antibody-positive PMN. This research was approved by the Ethics Committee of Peking University (No. IRB00001052-17018), written informed consent was not required under local legislation.

Patients with both IS and anti-PLA2R antibody-positive PMN treated in the Peking University First Hospital from January 2015 to December 2018 were enrolled in this study. All patients conformed to the diagnostic criteria of PMN clinically with serum anti-PLA2R antibody positivity. Eight patients were pathologically confirmed to have PMN. Serum anti-PLA2R antibody was measured by enzyme-linked immunosorbent assay test. PLA2R in glomerular deposition was measured by immunofluorescence assay.

All patients underwent cranial magnetic resonance imaging (MRI) on a 1.5- or 3.0-Tesla scanner. IS was verified through cranial MRI with or without ischemic attacks. We defined asymptomatic infarcts mainly by diffusion-weighted imaging. We reviewed the etiology of stroke in each patient and classified it using the Trial of Org 101172 in Acute Stroke Treatment system. Semi-quantitative analysis was used to detect correlations between PMN and neuroimaging characteristics. The global and total scores on the age-related white matter change (ARWMC) scale were used to evaluate the white matter lesions.

Among all patients with PMN who visited the Peking University First Hospital from January 2015 to December 2018, 14 patients developed IS. Of these 14 patients, 12/14 had anti-PLA2R antibody positivity and were enrolled in the study [Supplementary Table 1, http://links.lww.com/CM9/A155]. The mean anti-PLA2R antibody level was 97.3 ± 81.0 (range, 21–279) (relative unit, RU/ml). Risk factor screening of all 12 patients revealed hypertension in 10/12 patients, diabetes in 5/12, dyslipidemia in 9/12, hyperuricemia in 1/12, a smoking habit in 6/12, an alcohol-drinking habit in 4/12, and hypoalbuminemia in 9/12. Eight of 12 patients had an elevated D-dimer level. Nearly all patients had negative autoantibodies except that one patient (case 12) had positive antinuclear antibodies (ANA) test with a ratio 1:100.

Seven patients were followed up for 4 months to 3 years after discharge. All seven patients underwent normal treatment. At 12 months of follow-up (6 patients), none of these six patients reached complete remission (proteinuria of <0.3 g/24 h); however, one of 12 patients reached partial remission (proteinuria of <3.5 g/24 h).

Horizontal comparison of our patients vs. patients with anti-PLA2R antibody-positive PMN in the general population is shown in Supplementary Table 2,[2] http://links.lww.com/CM9/A156.
The mean age at onset of IS was 59.9 ± 12.2 (range, 45–78) years. At the time of IS onset, 4/12 patients were undergoing steroid or immunosuppressive therapy and 5/12 patients were undergoing diuretic therapy. Eleven of 12 patients were symptomatic: 8/12 presented with limb weakness or numbness as the initial symptom of IS, 2/12 presented with aphasia, 1/12 presented with central facial paralysis, 1/12 presented with dysarthria, 1/12 presented with dysgraphia, and 1/12 presented with dizziness. Two of the 12 patients (Patients 1 and 4) developed recurrence of IS. Patient 1 developed recurrence within 2 months after the first attack, and Patient 4 developed recurrence within 4 months after the first attack. In Patient 1, the recurrence developed while undergoing dabigatran therapy without obvious arterial stenosis [Figure 1].

Eleven of 12 patients had a small artery occlusion. The source of the embolism (non-cardiac) was identified in 6/12 patients on the basis of stroke in more than one vascular territory and a hypercoagulable state caused by PMN. Three of 12 patients had large artery atherosclerosis. Three of 12 patients were classified as having a stroke of undetermined etiology because of an incomplete vessel investigation. None of these patients had cardioembolism on the basis of normal Holter monitor and cardiac ultrasound.

We divided the etiology of IS into two groups: the embolism group (n = 6) and the large artery atherosclerosis group (n = 3). The median levels of serum anti-PLA2R antibody in embolism and large artery atherosclerosis groups were 88.5 and 84.0 RU/mL, respectively.

We detected the distribution of new and old infarctions by MRI in all patients [Supplementary Table 3, http://links.lww.com/CM9/A157]. All patients had subcortical infarction: the frontal lobe was affected in 11/12 patients, the parieto-occipital lobe in eight, and the temporal lobe in seven. Five of 12 patients had an infarction of the basal ganglia, five of the periventricular region, four of the infratentorial region (brain stem, n = 3; cerebellum, n = 2), and two of the corpus callosum. Eleven of 12 patients had an anterior circulation infarction and seven had a posterior infarction. The number of lacunar infarctions ranged from 0 to 16 (mean, 4.5 ± 5.0). The number of lacunar
infarctions presented no correlation with PAL2R values (Spearman $\rho = -0.575$, $P = 0.064$).

The ARWMC scores and the distribution of white matter change (WMC) in 11 of the 12 patients are shown in Supplementary Table 4, http://links.lww.com/CM9/A158. Eleven of 12 patients had WMC. The percentages of a global score of 0, 1, 2, and 3 were 0%, 36%, 18%, and 45%, respectively. The mean ARWMC total score was $7.8 \pm 5.0$ (range, 1–14). ARWMC total scores presented no correlation with PLA2R values (Spearman $\rho = 0.152$, $P = 0.655$). Eleven of 12 patients had WMC in the subcortical region, 11/12 in the frontal lobe, 7/12 in the parieto-occipital lobe, and 7/12 in the temporal lobe. Three of 12 patients had basal ganglia lesions and one had an infratentorial lesion.

Nearly all patients in our cohort had cerebral small vessel disease, especially WMC. We found two other main etiologies of IS: (1) non-cardiac embolism caused by a hypercoagulable state (suggested by high D-dimer value) of PMN and (2) large artery atherosclerosis, which might be caused by the severe lipometabolic disturbance in PMN. Therefore, multiple factors might be involved in the incidence of IS. None of the patients reported headache or showed autoantibody positivity. Therefore, the etiology of IS did not result from the combination of systemic vasculitis or other autoimmune diseases in patients with anti-PLA2R antibody-positive PMN.

Anti-PLA2R antibody is thought to be associated with the severity of PMN. In our cohort, we found anti-PLA2R antibody positivity in nearly 90% of patients with both PMN and IS, which is much higher than the rate of 58.8% among patients with PMN in our hospital, suggesting that a high anti-PLA2R antibody level might be a risk factor for IS. Moreover, in a previous study in Chinese people, an ARWMC global score of 2 was most common, while in our study, a global score of 3 was most prevalent. These data suggest that patients with anti-PLA2R antibody-positive PMN may develop more severe WMC. Studies with larger numbers of patients are needed to clarify this issue.

The recurrence rate among our patients was higher than that in the general population of patients with stroke in northern China (2/12 vs. 8.7%, respectively). The proportion of patients in our cohort who reached remission at the 12-month follow-up was 16.7%, compared with 58.2% among all anti-PLA2R antibody-positive patients. Hence, the occurrence of IS may suggest a poor prognosis of kidney disease. We found poor disease recovery and remission during follow-up, which might explain the sustainable high occurrence of IS.

IS is a rare complication of PMN. Traditional cardiovascular risk factors, especially diabetes mellitus and smoking, also seem to play an important role in the occurrence of stroke in anti-PLA2R antibody-positive patients. The severity of kidney disease might accelerate the development of IS. Cerebral small vessel disease, especially WMC, is a common feature of anti-PLA2R antibody-positive PMN, and non-cardiac embolism is the major etiology of IS. Multiple sub-cortical infarction in the anterior circulation is most prevalent, which differs from the general population of patients with IS. The severity of WMC might be correlated with positive anti-PLA2R antibodies, and a high level of anti-PLA2R antibodies might be a risk factor for IS. Patients with anti-PLA2R antibody positivity may have a higher rate of recurrence of IS, and the development of IS may suggest a poor prognosis of kidney disease.

Funding
This research was funded by a grant of the ULM-PUHSC Joint Institute for Translational and Clinical Research (No. PKU2017ZC001-5).

Conflicts of interest
None.

References
1. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41. doi: 10.1161/01.STR.24.1.35.

2. Jatem EE, Segarra MA, Carnicer CC, Martín-Gómez MA, Salcedo Allende MT, Ostoñ Roldán H, et al. Clinical features, course and prognosis of idiopathic membranous nephropathy depending on the presence of antibodies against M-type phospholipase A2 receptor. Nefrologia 2015;35:479–486. doi: 10.1016/j.nefro.2015.10.006.

3. Pang L, Zhang AM, Li HX, Du JL, Jiao LL, Duan N, et al. Serum anti-PLA2R antibody and glomerular PLA2R deposition in Chinese patients with membranous nephropathy: a cross-sectional study. Medicine (Baltimore) 2017;96:e7218. doi: 10.1097/MD.0000000000007218.

4. Xiong Y, Mok V, Wong A, Chen X, Chu WC, Fan Y, et al. The age-related white matter changes scale correlates with cognitive impairment. Eur J Neurol 2010;17:1451–1456. doi: 10.1111/j.1468-1331.2010.03078.x.

5. He Q, Wu C, Guo W, Wang ZY, Zhao YF, Lu J, et al. Hospital-based study of the frequency and risk factors of stroke recurrence in two years in China. J Stroke Cerebrovasc Dis 2017;26:2494–2500. doi: 10.1016/j.jstrokecerebrovasdis.2017.05.026.

6. Hoxha E, Thiele I, Zahnner G, Panzer U, Harendza S, Stahl RA, et al. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J Am Soc Nephrol 2014;25:1357–1366. doi: 10.1681/ASN.2013040430.

How to cite this article: Zhang J, Shu JL, You Q, Zhang W, Huang YN. Ischemic stroke in anti-phospholipase A2 receptor antibody-positive primary membranous nephropathy: clinical and neuromaging characteristics. Chin Med J 2020;133:361–363. doi: 10.1097/CM9.0000000000006010