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Longitudinal relationship between chronic kidney disease and distribution of cerebral microbleeds in patients with ischemic stroke

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ABSTRACT

Background: Chronic kidney disease (CKD) has been reported to be independently associated with cerebral microbleeds (CMB). Since both glomerular afferent arterioles and cerebral perforating arteries are strain vessels, CKD and CMB may share similar dynamic changes.
Objective: To clarify whether CKD and CKD progression are related to the distribution and evolution of CMB in patients with ischemic stroke.
Methods: We retrospectively examined the data from the CASISP study. 500 patients with ischemic stroke were analyzed. The number and distribution of CMB were assessed using Microbleed Anatomical Rating Scale. Renal function was evaluated by the estimated glomerular filtration rate (eGFR) and proteinuria.
Results: 51 (10.2%) and 158 (31.6%) had decreased eGFR (<60 ml/min/1.73 m^2) and CMB at baseline, respectively; 31 (6.6%) and 84 (16.8%) had CKD and CMB progression. Decreased eGFR at baseline (OR = 1.533, 95% CI: 1.111–2.114; p = 0.009), proteinuria (OR = 1.778, 95% CI: 1.026–3.083; p = 0.040), CKD progression (OR = 2.004, 95% CI: 1.191–3.370; p = 0.009) and history of hypertension (OR = 2.084, 95% CI: 1.241–3.49; p = 0.005) were independently associated with the presence of deep or infratentorial CMB at follow-up. CMB progression in deep or infratentorial area was more frequent in patients with CKD progression than those without (29.0% versus 13.1%, p = 0.028). Logistic regression analyses showed that CKD progression (OR = 2.577, 95% CI: 1.393–4.769; p = 0.003) was independently associated with the progression of deep or infratentorial CMB.
Conclusion: CKD and CKD progression are independently associated with presence and evolution of deep or infratentorial CMB, but not lobar CMB.

1. Introduction

Chronic kidney disease (CKD) is highly prevalent in stroke patients [1], and it has been viewed as a potential marker of small vessel disease [2,3] as well as a risk factor for stroke [4]. CKD often remains subclinical and is usually defined by a reduction in the glomerular filtration rate(GFR) or the presence of proteinuria.

Cerebral microbleeds (CMB) detected on magnetic resonance imaging (MRI) are generally considered to be clinically silent, but are regarded as a kind of cerebral small vessel disease which is prone to bleeding. The pathological abnormalities are old blood leakage through fragile small vessels mainly affected by hypertensive arteriopathy including lipofibrohyalinosis and arteriolosclerosis (most commonly involving deep structures) or cerebral amyloid angiopathy (typically lobar locations) [5,6].

Several studies have demonstrated the association of CKD with CMB in different cohorts [7,8]. However, it is unclear whether CKD is a risk factor for CMB or CKD just coexists with CMB. CMB are more frequently present in patients with end-stage renal disease than in those without [9]. One cross-sectional study also found that advanced CKD stage was associated with increased prevalence of CMB [10]. So we hypothesized that CKD progression would be associated with deterioration of CMB load.

So far, no study has targeted the association between dynamic changes of CKD and CMB. The objective of the present study was to clarify whether CKD and CKD progression are related to the presence, distribution and evolution of CMB in patients with ischemic stroke.

2. Methods

2.1. Subjects

All the data originated from CASISP study (Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention, registration number NCT00202020 at Clinical Trials.gov) as previous report [11]. Patients with an ischemic stroke confirmed by brain CT or MRI within the previous 1 to 6 months were enrolled consecutively from May 2004 to December 2004, and were followed-up every month for 12 to

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18 months. All the patients should have modified Rankin Scale <4 at the time of enrollment with informed consent. The exclusion criteria include: 1. History of intracranial hemorrhage; 2. Cardiogenic embolism; 3. Uncontrolled severe hypertension (>180/120 mm Hg); 4. Severe comorbidities such as end stage renal disease, liver cirrhosis, and heart failure; 5. Contraindications to antiplatelet treatment or MRI check. The study was approved by Ethics Committee of Peking University First Hospital (Approval number: Clinical Trial 2004-11).

Clinical information obtained at baseline included the patient's risk factors, blood pressure, National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale. Routine blood and urine tests were assessed at enrollment, month 3, month 6 and the end of the study. During follow-up, all the patients received state-of-the-art therapy for secondary stroke prevention, including antiplatelet agents, antihypertensive agents, antidiabetics and statins therapy.

2.2. Magnetic resonance imaging

Brain MRI was performed on a 1.5 T magnet system with a standard quadrature head coil both at the beginning and the end of the study. MR sequences were obtained in the axial plane with the following parameters: slice thickness/gap = 6 mm/1–2 mm, T1 (TR/TE = 400–2280 ms/8–27 ms), T2 (TR/TE = 3000–4800 ms/80–120 ms), FLAIR (TR/TE = 5000–11,000 ms/100–146 ms), DWI(TR/TE = 3000–10,000 ms/45–112 ms), and T2 gradient echo imaging (T2*, TR/TE = 300–545 ms/3.5–23 ms, flip angle = 26°). CMB were defined as small foci of signal loss or hypointensity on T2*-weighted MRI. A trained neurologist (blind to clinical data) counted CMB in deep, lobar, and infratentorial regions respectively using the Microbleed Anatomic Rating Scale (MARS) [12]. A higher score of MARS by the end of the study was considered as CMB progression. The inter-rater reliability was determined by tests using MARS (kappa = 0.94) scale for 20 random scans. Patients with ≥1 deep or infartentorial microbleeds were counted as having deep or infratentorial microbleeds regardless of whether they had lobar microbleeds.

2.3. Estimation of kidney function

eGFR was calculated with an equation developed by adaptation of the Modification of Diet in Renal Disease(MDRD) formula on the basis of data from Chinese chronic kidney disease patients [13]: eGFR (ml/min/1.73 m^2) = 175 × (serum creatinine [mg/dl]$^{-1.234}$ × (age [years])$^{-0.179}$ × (0.79 for women).

GFR categories were assigned as follows: G1 normal eGFR ≥ 90 ml/min/1.73 m^2; G2 mildly decreased eGFR 60–89 ml/min/1.73 m^2; G3 moderately decreased eGFR 30–59 ml/min/1.73 m^2, according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative classification and staging system [14]. Impaired kidney function was defined as eGFR < 60 ml/min/1.73 m^2. Progression of CKD is defined as a drop in eGFR category accompanied by a 25% or greater drop in eGFR from baseline [14].

Reagent strip urinalysis for total protein with automated reading was used for testing of proteinuria. Urine protein was recorded as negative (less than 10 mg/dL), trace (10 to 20 mg/dL), 1 + (30 mg/dL), 2 + (100 mg/dL), 3 + (300 mg/dL), 4 + (1000 mg/dL). More than twice positive during the follow-up was regarded as proteinuria.

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 13.0 statistical software. All data are expressed as the mean ± SD. Independent t-test and χ^2 test were applied respectively to compare the continuous variables and the categorical variables. Nonparametric test was used to compare difference of NIHSS between two groups. The independent risk factors for CMB presence in different regions were investigated by binary logistic regression. Logistic regression analysis was also used to evaluate the association between CKD development and CMB progression in different location during follow-up. The following factors were entered into the logistic regression: age, sex, history of hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, coronary heart disease and smoking, use of statins, antihypertensive drugs and antiplatelet drugs, presence of proteinuria, impaired kidney function at baseline, and CKD progression. All tests were two-tailed and a P value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of 720 participants at baseline recruitment, 597 subjects finished the follow-up and underwent a second MRI at the end of the study (Fig. 1). For those 597 patients, 97 were excluded because of different magnetic field strength or lack of previous comparable T2* imaging. All of the 500 patients had baseline kidney function, while 3 of them missed serum creatinine check at the end of the study. There were no significant differences among demographic and risk factors between included and excluded patients (Table 1). For the 500 subjects, the mean systolic/diastolic blood pressure was 137.1 ± 17.1/83.3 ± 10.4 mm Hg at baseline, and 132.7 ± 14.4/80.5 ± 9.0 mm Hg at follow-up. Baseline demographic and clinical characteristics between patients with CMB versus those without are shown in Table 2.

3.2. Presence and progression of CMB

158 patients (31.6%) had ≥1 CMB lesions at baseline, out of 500 subjects with follow-up T2* imaging. 139 (27.8%) had deep or infratentorial CMB, while 79 (15.8%) had lobar CMB. Over a median of 14 months of follow-up, new and developing CMB were visible in 84 (16.8%) patients, including new CMB in 25 (5.0%) and a greater MARS score than at baseline in 59 11.8%). Among 84 patients with CMB progression, 46 patients (17.7%) were in the aspirin therapy group and 38 patients (15.8%) were in the cilostazol therapy group. There was no significant association between CMB progression and antiplatelet drugs (p = 0.579). The CMB lesion load increased in deep areas in 56 subjects, in lobar areas in 36 subjects, and in infratentorial areas in 23 subjects.

3.3. Kidney function and its dynamic change

Average eGFR was 86.4 ± 22.9 mL/min/1.73 m^2 at baseline versus 82.9 ± 21.9 mL/min/1.73 m^2 at the end of the study(p < 0.001). Table 3 shows GFR categories at baseline and the end of the study (p = 0.093). 303 (60.6%) and 334 (67.2%) patients had eGFR <90 mL/min/1.73 m^2 at baseline and the follow-up, respectively (p = 0.030). 75 patients had proteinuria. For the 51 patients with impaired kidney function at baseline, the mean systolic/diastolic blood pressure were 136.7 ± 16.9/83.4 ± 10.4 mm Hg at baseline, not significantly different from those of others (140.9 ± 18.1/82.7 ± 10.2 mm Hg, p = 0.097, 0.680). Over the 14 months follow-up, 31 patients (6.6%) had progression of CKD. Among the 31 patients, 17 patients (6.7%) were in the aspirin group and 14 patients(5.7%) were in the cilostazol group (p = 0.676). For the patients with/without CKD progression, the mean systolic and diastolic blood pressure were 137.6 ± 17.3/136.8 ± 16.8 (p = 0.704) and 83.5 ± 10.6/83.1 ± 10.2 mm Hg (p = 0.742) at baseline, 133.9 ± 12.9/132.5 ± 14.7 (p = 0.393) and 80.1 ± 9.6/80.5 ± 8.9 mm Hg (p = 0.718) at follow-up.

3.4. Association of CKD and presence of CMB in different regions

The presence of CMB was much higher in patients with impaired kidney function than the other patients with eGFR ≥60 mL/min/1.73 m^2 both at baseline (26/51, 51.0% versus 132/449, 29.4%, p = 0.002) and at the follow-up(30/58, 51.7% versus 139/439, 31.7%, p =