Chronic Kidney Disease in Patients With Lacunar Stroke
Association With Enlarged Perivascular Spaces and Total Magnetic Resonance Imaging Burden of Cerebral Small Vessel Disease

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Background and Purpose—The relationship between chronic kidney disease and cerebral small vessel disease (cSVD), especially enlarged perivascular spaces (EPVS), has not been fully understood. This study aimed to investigate the association of chronic kidney disease and EPVS, as well as the total burden of cSVD on magnetic resonance imaging, expressed by the simultaneous presence of multiple markers of cSVD, among patients with first-ever lacunar stroke.

Methods—Four hundred and thirteen consecutive patients were prospectively enrolled. Centrum semiovale and basal ganglia EPVS on T2-weighted magnetic resonance imaging, as well as other imaging markers of cSVD, including lacune, white matter lesions, and cerebral microbleeds, were rated using validated scales. Chronic kidney disease was defined as either reduced estimated glomerular filtration rate or the presence of proteinuria.

Results—After adjustments for potential confounders by logistic regression, proteinuria and impaired estimated glomerular filtration rate were correlated with the severity of EPVS in both centrum semiovale (odds ratio [OR] 2.59; 95% confidence interval [CI] 1.19–5.64 and OR 2.37; 95% CI 1.19–4.73) and basal ganglia (OR 5.12; 95% CI 2.70–12.10 and OR 4.17; 95% CI 2.08–8.37). A similar association was also found between proteinuria and low estimated glomerular filtration rate levels and the comprehensive cSVD burden (OR 2.13; 95% CI 1.10–4.14 and OR 5.59; 95% CI 2.58–12.08).

Conclusions—Proteinuria and impaired estimated glomerular filtration rate are associated with increasing EPVS severity and, furthermore, accumulated magnetic resonance imaging burden of cSVD in patients with first-ever acute lacunar stroke. (Stroke. 2015;46:2081-2086. DOI: 10.1161/STROKEAHA.114.008155.)

Key Words: cerebral small vessel disease ■ enlarged perivascular spaces ■ glomerular filtration rate ■ proteinuria

Chronic kidney disease (CKD), as an important public health problem, affects 10% to 15% of the general adult population.1–4 It was commonly defined by a reduction in the estimated glomerular filtration rate (eGFR) or the presence of proteinuria.4 Increasing evidence links CKD to higher risk and mortality of cerebrovascular disease because both human brain and kidney are low-resistance-end arterial organs allowing continuous and passive high-volume perfusion throughout systole and diastole.5–7 Of the many pathophysiological mechanisms underlying cerebrovascular disease, small vessel microangiopathy would presumably be the type with the strongest association with impaired kidney function because the microvasculature of both organs share anatomic and functional vasoregulatory similarities.8

Previous studies have indicated that CKD correlates with a higher prevalence of white matter hyperintensities (WMH), lacune, and cerebral microbleeds (CMBs).9–11 However, the association between CKD and enlarged perivascular spaces (EPVS), a novel marker of cerebral small vessel disease (cSVD), has not yet been clarified. Furthermore, the combined effect of these magnetic resonance imaging (MRI) markers of cSVD on impaired kidney function has never been studied. It seems rather artificial to over-reliance on one marker only while disregarding the others.12–15
Thus, we aimed to clarify the association of CKD with EPVS severity and the total burden of cSVD on MRI in patients with first-ever lacunar stroke.

Methods

Patients

We prospectively recruited patients with first-ever lacunar stroke in the department of neurology at Jinling hospital. Details of patient inclusion can be found in the online-only Data Supplement. All patients had a detailed diagnostic assessment that included neurological investigations, blood pressure measurements, MRI (unless contraindicated), blood tests, and urine tests. In this study, lacunar stroke was defined as an acute lacunar stroke syndrome with a small (maximum diameter of 15 mm), deep infarct on MRI compatible with the clinical findings, or, if no such lesion was visible, we used established criteria of specific clinical lacunar syndromes. Because we aimed to study patients who most likely had their stroke from local cSVD, patients with a possible cardioembolic source (most commonly atrial fibrillation or a valvular prosthesis) or large-vessel cerebrovascular disease defined as internal carotid, middle cerebral, or basilar intracranial artery stenosis >50% were excluded. Informed consent was obtained from all participants, and the study protocol was approved by the institutional Human Research Ethics Committee of Jinling Hospital.

Measurement of the eGFR and Proteinuria

eGFR was calculated individually by the following Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for the Asian population: eGFR = 141×min (serum creatinine/κ,1)×max (serum creatinine/κ,1)^−1.20×0.993^×1.018 [if female], where κ = 0.7 for females and 0.9 for males, α = −0.329 for females and −0.411 for males, κ was the minimum of S/CR or 1, and α indicated the maximum of S/CR or 1. A low eGFR level was defined as <60 mL/min/1.73 m^2, which shows a moderate stage of CKD. Proteinuria was measured from the first morning urine sample, using a urine dipstick test. Urine protein was recorded as negative (<10 mg/dL), trace (10–30 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ (1000 mg/dL). Urinary protein on admission was analyzed by the hospital’s laboratory using the Sysmex UF-1000i urine analyzer (TOA Medical Electronics, Kobe, Japan).

MRI Protocol and Assessment

MRI was performed on a 3.0-T whole-body MRI system (Magnetom Trio, Siemens, Erlangen, Germany) to obtain axial T1-weighted, axial T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging, and axial susceptibility-weighted imaging.

The imaging markers and burden scale of SVD were defined as below.

Enlarged Perivascular Spaces

We define perivascular spaces as round, oval, or linear-shaped lesions with signal intensity similar to that of cerebrospinal fluid on all sequence spaces and without a T2-hyperintense rim on FLAIR imaging. EPVS were rated in centrum semiovale and basal ganglia regions. At both levels, we identified the slide in the most affected hemisphere only. The number of EPVS was rated as follows: 0 to 10 EPVS (category 1); 11 to 25 EPVS (category 2); and ≥25 EPVS (category 3) at both anatomical areas. For counting the total burden of cSVD, we only counted EPVS at the level of the basal ganglia because EPVS at this level are specifically related to cSVD.

Brain Atrophy

Brain atrophy was evaluated using the voxel-based specific regional analysis system, which has been validated and described in detail elsewhere. The brain atrophy index was calculated as the proportion of the number of atrophic voxels relative to the total number of voxels of the entire brain.

Cerebral Small Vessel Disease Burden Scale

The cSVD burden scale incorporating 4 MRI markers of cSVD (lacune, WMH, CMBs, and EPVS) was described in detail elsewhere. Briefly, lacune were identified as a round or ovoid hyperintense lesions, of between 3 and 15 mm in diameter, on T2-weighted images with a surrounding rim of hyperintensity on FLAIR and not compatible with the clinical stroke. WMH were rated using the modified Fazekas scale on FLAIR images, and further volumetric information of WMH were assessed by commercially available software. CMBs were defined on susceptibility-weighted imaging as homogenous rounded lesions of signal loss, within a diameter <10 mm. An ordinal score ranging from 0 to 4 was constructed to reflect the total cSVD burden. One point was awarded for each of the following items: moderate to extensive (10–25 or >25) EPVS in the basal ganglia (1 point if present); ≥1 asymptomatic lacune (1 point if present); periventricular WMH Fazekas score 3 or if deep WMH Fazekas score 2 or 3 (1 point if present); ≥1 deep CMBs (1 point if present) as the available evidence suggests that specifically deep CMBs are related to cSVD. Limited intrarater reliability testing (50 scans) showed a good reliability with kappa values of 0.83 for basal ganglia EPVS, 0.79 for centrum semiovale EPVS, 0.74 for the presence of lacune, 0.84 for deep CMBs, and 0.77 for deep WMH.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL). We dichotomized centrum semiovale- and basal ganglia EPVS into degrees 1 (category 1) and degrees 2–3 (category 2, category 3), reflecting mild versus moderate/severe EPVS. Differences in baseline characteristics between the severity groups of EPVS in different regions also increasing cSVD burden groups were determined using χ^2 analysis of variance, or Kruskal–Wallis where appropriate. Logistic regression was used to assess the relationship between cSVD (eGFR level or proteinuria) and the severity of EPVS in different regions as a binary variable. For the analysis of cSVD burden scale as an ordinal outcome, we used ordinal logistic regression model. All multivariable analyses were first adjusted for age and sex (Model 1) and additionally adjusted for all variables (including age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoker, antithrombotic treatment, and brain atrophy index; Model 2). For purposes of these analyses, proteinuria grades were dichotomized into a binary variable by incorporating no proteinuria and trace into a single category and proteinuria grades 1+, 2+, 3+, and 4+ into another category. The relationship between cSVD burden scale as an ordinal outcome can occur during acute stress, infections, or dehydration sometimes, we do the former to accommodate the potential false-positive result of trace proteinuria. In the case of the latter, the individual with proteinuria grades 1+, 2+, 3+, and 4+ were relatively less frequent. Additionally, eGFR values were also categorized into 2 categories: <60 and ≥60 mL/min/1.73 m^2. All tests were two-tailed and values of P<0.05 were considered statistically significant.

Results

Patient Characteristics

Finally, 413 patients (mean age, 64.41±9.43 years; 63.0% male) with lacunar ischemic stroke were enrolled in this study (Figure I in the online-only Data Supplement). Demographic and clinical characteristics between patients included and patients excluded are presented in Table I in the online-only Data Supplement. Among these patients, 72.4% had hypertension, 23.0% had diabetes mellitus, 51.6% had hyperlipidemia, 40.2% of subjects had EPVS of degree 2 or 3 in the centrum semiovale and 42.1% in the basal ganglia. For cSVD burden, 85 patients (20.6%) had no markers of cSVD and 25 patients (6.1%) presented with all 4 markers.
EPVS and Total Burden of cSVD on MRI

Table 1 presents the relevant characteristics for the different subgroups based on the severity of EPVS at the centrum semiovale and basal ganglia. Higher numbers of EPVS at the centrum semiovale and basal ganglia were related to increasing age, as well as to the presence of hypertension, other cSVD markers (Lacune, WMH, CMBs, and brain atrophy index), high proteinuria grade, and low eGFR levels. Table 2 shows the characteristics of the study population stratified by the total burden of cSVD. Age, hypertension, brain atrophy index, eGFR values, and proteinuria grade differed significantly with increasing categories (0–4) of total burden of cSVD. Sex and the presence of vascular risk factors did not differ significantly among categories.

Association of CKD With EPVS and Total Burden of cSVD

Of the 413 patients, 87 (21.1%) patients had an eGFR <60 mL/min/1.73 m². Among them, 35 patients had diabetic CKD, 22 patients had chronic glomerulonephritis, 7 patients had hypertension-related CKD, and the other 23 patients had unknown etiologies without biopsy. Table 3 summarizes the results of the binary logistic regression of the EPVS and the ordinal logistic regression of the total burden of cSVD. Low eGFR levels and elevated protein in the urine were significantly associated with EPVS in the 2 anatomic areas (centrum semiovale and basal ganglia) and an increasing number of different markers of cSVD, with adjustment for age and sex (Table 3). After adjusting for all confounders, both low eGFR and elevated proteinuria were related with presence of centrum semiovale EPVS (odds ratio [OR] 2.37, 95% confidence interval [CI] 1.19–4.73 and OR 2.59, 95% CI 1.19–5.64, respectively) or basal ganglia EPVS (OR 4.17, 95% CI 2.08 to 8.37 and OR 5.12 95% CI 2.70 to 12.10, respectively; Table 3).

For the test of ordinal logistic regression analysis, we also found similar associations between cSVD category and these 2 measures of kidney disease. EGFR (OR 5.59, 95% CI 2.58–12.08) and proteinuria (OR 2.13, 95% CI 1.10–4.14) remained as independent predictors for increasing burden of cSVD burden after adjusting for all confounding variables.

Discussion

In this study, we demonstrated that decreased eGFR and elevated urine protein were associated with both the severity of EPVS and the increasing cSVD burden, expressed by the co-occurrence of 4 different markers.

The association between proteinuria and the presence and extent of WMH or CMBs has been extensively investigated, as well as the association between eGFR and lacune, WMH, or CMBs. However, no studies are available to date investigating the association of CKD with EPVS, which is a novel marker of cSVD. Our study demonstrated similar association between EPVS and kidney disorder, further highlighting the similarities between cSVD and kidney disorders.

Table 1. Characteristics of Subgroups Based on the Severity of EPVS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Centrum Semiovale EPVS</th>
<th>Basal Ganglia EPVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degrees 1</td>
<td>Degrees 2+3</td>
<td>Degrees 1</td>
</tr>
<tr>
<td>N, %</td>
<td>247 (59.8)</td>
<td>166 (40.2)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>59.9±7.8</td>
<td>71.2±7.3</td>
</tr>
<tr>
<td>Female, %</td>
<td>89 (36.0)</td>
<td>64 (38.6)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>158 (64.0)</td>
<td>141 (84.9)</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>130 (52.6)</td>
<td>83 (50.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>58 (23.5)</td>
<td>37 (22.3)</td>
</tr>
<tr>
<td>Antithrombotic treatment</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Mono antiplatelets, %</td>
<td>121 (49.0)</td>
<td>85 (51.2)</td>
</tr>
<tr>
<td>Dual antiplatelets, %</td>
<td>114 (46.2)</td>
<td>68 (41.0)</td>
</tr>
<tr>
<td>Anticoagulants, %</td>
<td>12 (4.9)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>95 (38.5)</td>
<td>55 (33.1)</td>
</tr>
<tr>
<td>Brain atrophy index, %, median (IQR)</td>
<td>1.7 (1.2)</td>
<td>5.2 (3.9)</td>
</tr>
<tr>
<td>Lacune, %</td>
<td>112 (45.3)</td>
<td>108 (65.1)</td>
</tr>
<tr>
<td>WMH, mL, mean (SD)</td>
<td>4.2±1.1</td>
<td>9.9±3.6</td>
</tr>
<tr>
<td>CMBs, %</td>
<td>29 (11.7)</td>
<td>65 (39.2)</td>
</tr>
<tr>
<td>Proteinuria grade</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Trace, %</td>
<td>96 (38.9)</td>
<td>48 (28.9)</td>
</tr>
<tr>
<td>1+, %</td>
<td>11 (4.5)</td>
<td>26 (15.7)</td>
</tr>
<tr>
<td>2+, %</td>
<td>7 (2.8)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>3+, %</td>
<td>3 (1.2)</td>
<td>24 (14.5)</td>
</tr>
<tr>
<td>4+, %</td>
<td>4 (1.6)</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m², %</td>
<td>19 (7.7)</td>
<td>68 (41.0)</td>
</tr>
</tbody>
</table>

CMBs indicates cerebral microbleeds; eGFR, estimated glomerular filtration rate; EPVS, enlarged perivascular spaces; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; and WMH, white matter hyperintensity.
Furthermore, we also demonstrated that proteinuria and decreased eGFR, 2 markers of CKD were associated with the total burden of cSVD, extending the previous studies mainly focusing on the individual cSVD features, not the combined components as one disorder. In addition, it might be speculated that eGFR and proteinuria reflect a more generalized process indicative of underlying vascular damage, not limited to the kidney disease.

The vascular beds of the human brain and kidney share anatomic and hemodynamic similarities. Therefore, early surrogate markers of kidney function impairment may also serve as early indicators of vascular brain damage. In consequence of anatomic and vasoregulatory similarities of the human brain and kidney, both organs might have a common soil of pathogenesis. They share common vascular risk factors (ie, hypertension and diabetes mellitus), so therapies focusing on the rigorous control of cSVD-related risk factors may have preventive implications to protect against multiple organ dysfunction in patients at risk.

According to a recent review on neuroimaging insights of cSVD, approaches to assess the total cSVD load on imaging are needed. After a first attempt by Staals et al, although this cSVD scale that adopted in our study have some limitations, such as ignore the location and extent of each cSVD marker, it is easy to use and basically capture total brain damage resulting from cSVD. Positive associations of decreased cognitive function and higher ambulatory blood pressure levels to accumulation of MRI markers have already been demonstrated. Further studies on cSVD are now also needed to take into account the total SVD load, avoiding over-reliance on just one feature as in most previous studies.

Brain atrophy is sometimes considered as another potentially MRI feature of cSVD. Although many studies have suggested an association between brain atrophy and cSVD, it is

| Table 3. eGFR Levels and Proteinuria In relation to EPVS and the Total Burden of Cerebral Small Vessel Disease |
|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
|                                         | Centrum Semiovale EPVS OR (95% CI)       | Basal Ganglia EPVS OR (95% CI)           | cSVD Burden OR (95% CI)                  |
|                                         | Model 1                                  | Model 2                                  | Model 3                                  | Model 4                                  |
| eGFR (≤60 mL/min/1.73 m² vs >60 mL/min/1.73 m²) | 2.54 (1.35–4.79)*                        | 2.37 (1.19–4.73)*                        | 3.45 (1.85–6.40)†                       | 4.17 (2.08–8.37)†                       |
| Protein in urine (1–4+ vs trace/absent)  | 2.57 (1.37–4.83)*                        | 2.59 (1.19–5.64)*                        | 3.61 (2.00–6.50)†                       | 5.12 (2.70–12.10)†                      |
|                                          |                                          |                                          |                                          |                                          |
|                                          |                                          |                                          |                                          |                                          |

Model 1: bivariate logistic regression analyses with adjustment for age and sex. Model 2: bivariate logistic regression analyses with adjustment for all variables (including age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoker, antithrombotic treatment, Lacune, WMH, CMBs, and brain atrophy index). Model 3: ordinal regression analyses with adjustment for age and sex. Model 4: ordinal logistic regression analyses with adjustment for all variables (including age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoker, antithrombotic treatment and brain atrophy index). CI indicates confidence interval; cSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate; EPVS, enlarged perivascular spaces; OR, odds ratio; and WMH, white matter hyperintensity.

*P<0.05.
†P=0.001.
not specific to cSVD, often occurring in many other conditions. Besides, it is definitely inappropriate to arbitrarily assign further points to the scale without validation. Therefore, our existing scale did not include brain atrophy in the total cSVD score. It is not uncommon that patients with a first-ever lacunar infarct have mild cognitive impairment and presence of lacunar infarct may be a predictor of subcortical vascular dementia in the medium–long term. Longitudinal studies evaluating the progression of cSVD and neuropsychological insights into the long-term effects of renal dysfunction are needed. Furthermore, it is worthy to note that the indices of renal function were only analyzed during the acute phase of ischemic stroke. Ideally, it would be preferable to assess renal function beyond the acute phase to alleviate the influence of the acute phase reaction, but ethically it is unreasonable for patients with kidney dysfunction to be left untreated during the hospitalization. And it is also difficult to standardize treatment to meet all patients’ needs. In this perspective, potential biases might be more pronounced if the post-treated eGFR and proteinuria were adopted.

The main strength of our study is that we collected a homogeneous group of lacunar stroke patients, with a substantial prevalence of MRI markers of cSVD, which makes this group suitable for studying the association between EPVS, total burden of cSVD, and impaired kidney function. Also, the sociodemographic and clinical information of all patients was collected in a prospective fashion. Nonetheless, several limitations of the present study were listed below. First, proteinuria was determined from a single urine sample, whereas, ideally, it would have been determined in multiple samples. Second, kidney function was assessed using serum creatinine–derived equations only. However, the CKD–EPI equation is also widely accepted as a valid surrogate of kidney function for the Asian population. Third, the CKD–EPI equation was given the convenience of clinical use, WMH were rated using a semiquantitative rating scale, although this scale is widely used with a good sensitivity and reliability and fits for the existing cSVD burden scale. Fourth, our patient selection favors less disabled patients, able to undergo MRI. The selection bias would probably lead to an underestimation of the association between the severity of EPVS and total burden of cSVD and impaired kidney function.

In conclusion, our findings suggest that the presence of proteinuria and decreased eGFR levels are associated with the severity of EPVS and an increasing total burden of cSVD in patients with lacunar stroke. Longitudinal studies are required to confirm the causal relationship between CKD and cSVD.

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Disclosures
None.

References


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SUPPLEMENTAL MATERIAL

Chronic kidney disease in patients with lacunar stroke: association with enlarged perivascular spaces and total MRI burden of cerebral small vessel disease
Supplemental Methods

Figure I Flow chart of patient inclusion.

Consecutive patients with recent first-ever lacunar stroke (N=655)

Patients selected in this study (N=468)

Exclusion: (N=187)
- 158 History of stroke or TIA
- 29 Incomplete MRI examination

Further Exclusion: (N=55)
- Symptomatic large artery occlusion (>50%)
  - 25 Internal carotid artery
  - 14 Middle cerebral artery
  - 4 Basilar artery
- Possible cardioembolic source (N=12)

Patients included in final analysis (N=413)

Figure 1: Flow chart of patient inclusion. TIA, transient ischemic attack.
Supplemental Table I. Demographic and clinical characteristics of included and excluded patients

<table>
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<tr>
<th>Characteristics</th>
<th>Patients included</th>
<th>Patients excluded</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>413 (63.1)</td>
<td>242 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, year</td>
<td>64.41 ± 9.43</td>
<td>64.89 ± 10.24</td>
<td>0.56</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>153 (37.0)</td>
<td>103 (42.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>299 (72.4)</td>
<td>171 (70.7)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hyperlipidemia, (%)</td>
<td>213 (51.6)</td>
<td>139 (57.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes Mellitus, (%)</td>
<td>95 (23.0)</td>
<td>62 (25.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Current smoker, (%)</td>
<td>150 (36.3)</td>
<td>73 (30.2)</td>
<td>0.11</td>
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</tbody>
</table>

SD denotes Standard Deviation