Deep Cerebral Microbleeds and Renal Dysfunction in Patients with Acute Lacunar Infarcts

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Background: Cerebral small-vessel disease (SVD) is associated with renal dysfunction such as chronic kidney disease. Although cerebral microbleeds (CMBs) are common in patients with acute lacunar infarcts (ALI), the association between renal dysfunction and CMBs in such patients remains unclear. *Methods:* Between April 2007 and March 2013, we evaluated consecutive first-ever ALI patients, who were admitted to our hospital within 24 hours of stroke onset. CMBs were defined as focal areas of signal loss in brain parenchyma less than 5 mm on T2*-weighted gradient-echo imaging. Renal dysfunction was defined as an estimated glomerular filtration rate less than 60 mL/minute/1.73 m^2 on admission. Correlations between renal dysfunction and the presence (model 1) and location of CMBs (model 2; any deep or infratentorial CMBs) were determined by multivariable logistic regression analyses. *Results:* Among 152 patients (33.6% men; mean age, 67.6 years), 53 had CMBs. Patients with CMBs were older (69.9 versus 66.3 years, $P = .03$) and had a higher frequency of white matter hyperintensity (WMH; 62.3% versus 25.3%, $P < .001$), silent lacunar infarcts (SLI; 75.5% versus 43.3%, $P < .001$), and renal dysfunction (41.5% versus 22.2%, $P = .015$) than those without CMBs. On multivariable analyses, renal dysfunction (odds ratio, 95% confidence interval; model 1: 2.38, 1.02-5.66; model 2: 2.78, 1.16-6.81), WMH (3.87, 1.76-8.80; 3.72, 1.64-8.71), SLI (3.85, 1.71-9.14; 4.20, 1.77-10.8), and diabetes mellitus (.26, .09-.63; .24, .08-.63) were independently associated with CMBs. *Conclusions:* In patients with ALI, renal dysfunction was positively associated with CMBs independent of cerebral SVD. **Key Words:** Cerebral microbleeds—chronic kidney disease—lacunar infarcts—renal dysfunction—small vessel disease—stroke.

Cerebral microbleeds (CMBs), defined as small, focal, hypointense lesions on T2*-weighted gradient-echo magnetic resonance imaging (MRI), are common in patients with stroke and in community-dwelling older adults.[1] Although CMBs in a lobar location are associated with cerebral amyloid angiopathy, most CMBs in the basal ganglia are associated with hypertensive vasculopathy, which has been implicated in cerebral small-vessel disease (SVD).[2] In addition to stroke, cerebral SVD, such as acute lacunar infarcts (ALI) and white matter hyperintensity (WMH), has been focused on because of its association with both stroke and dementia, which could be a burden for long-term care.[1-4]

Previous studies showed the associations between cerebral SVD and renal dysfunction, such as chronic kidney

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disease.[5-7] Although renal dysfunction is associated with CMBs in patients with ischemic stroke[8,9] and patients with hemorrhagic stroke,[10] this association has not been fully clarified yet. Furthermore, renal dysfunction is also associated with cardioembolic stroke.[11] Hence, the strict analysis of selected patients using detailed stroke subtypes could clarify such association. We have recently demonstrated the association between cerebral SVD and renal dysfunction in patients with stroke[12]; however, the independent association between renal dysfunction and CMBs in patients with ALI remains unclear. The aim of this study was to investigate the characteristics of CMBs stratified by the numbers and the locations and to explore whether renal dysfunction is independently associated with CMBs in patients with ALI.

Materials and Methods

Study Design

Between April 2007 and March 2013, we enrolled consecutive patients with first-ever ALI who were admitted to our hospital within 24 hours of stroke onset. An eligible infarct size was defined as a lesion less than 15 mm in diameter detected on diffusion-weighted imaging (DWI) scans on admission according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[13] Patients with atrial fibrillation and/or recurrent stroke were excluded to ensure the homogeneity of the cohort. This cross-sectional study complied with the Declaration of Helsinki and was approved by the Institutional Review Board at the Kawasaki Medical School Hospital. Informed consent was obtained from all patients. This trial is registered at the UMIN Clinical Trials Registry (UMIN000013555).

Assessments

We assessed age, sex, body mass index, blood pressure, and laboratory data on admission. Neurologists assessed the National Institutes of Health Stroke Scale scores on admission and at discharge, as a measure of stroke severity. The modified Rankin Scale scores were assessed at 90 days after the stroke onset as a measure of stroke outcome, and modified Rankin Scale scores of 0 to 2 were defined as a good outcome and scores of 3 to 5 as a poor outcome.[14] Stroke subtype was classified according to the TOAST criteria.[13] Risk factors were identified as follows: (1) hypertension, a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more and/or the use of antihypertensive agents; (2) dyslipidemia, a total serum cholesterol level of 220 mg/dL or more and/or the use of statins; (3) diabetes mellitus (DM), a hemoglobin A1c (HbA_{1c}) level of 6.5% or more and/or the use of oral hypoglycemic agents or insulin, and/or a serum fasting glucose level of 126 mg/dL or more; (4) ischemic heart disease, a history of physician-diagnosed angina pectoris, evidence of prior myocardial infarction or a prior coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass surgery). Current smoking habits and alcohol consumption were assessed on admission.

Renal Dysfunction

Serum creatinine was measured on admission, and estimated glomerular filtration rate (eGFR) was determined using the equation proposed by the Japanese Society of Nephrology as follows: eGFR (mL/minute/1.73 m^2) = 194 × (serum creatinine [mg/dL])$^{-1.094}$ × (age [year])$^{-.287}$ × .739 (if female).[11] Renal dysfunction was defined as eGFR less than 60 mL/minute/1.73 m^2 on admission.[6,12]

Magnetic Resonance Imaging

Patients underwent a 1.5-T MRI of the brain (Signa EXCITE XL version 11.0; GE Healthcare, Milwaukee, WI), including DWI, fluid-attenuated inversion recovery (FLAIR) imaging, T2*-weighted gradient-echo imaging, and three-dimensional time-of-flight MR angiography. The neuroimaging protocol has been described in detail previously.[12] One trained neurologist (N.S.) assessed all of the MR images and was blind to all other patient data. ALI was defined as a lesion less than 15 mm in diameter detected by DWI scans on admission.[13] Silent lacunar infarct (SLI) was defined as a focal lesion of at least 3 mm in diameter, with hyperintensity on T2WI and hypointensity on FLAIR images.[15-18] WMH was defined as an irregular periventricular hyperintensity (Fazekas grade ≥3) and/or early confluent or separate, confluent, deep WMH lesions (Fazekas grade ≥2) on T2WI and FLAIR images.[15-18] CMBs were defined as focal areas of signal loss in brain parenchyma less than 5 mm in diameter on T2*-weighted gradient-echo imaging scans.[1-19] We categorized the locations of CMBs as follows: lobar (cortex and white matter), deep (basal ganglia; thalamus; and internal, external, or extreme capsule), infratentorial (cerebellum and brain stem), and combined (both deep and lobar).[20] Symmetrical basal ganglia calcifications and flow void artifacts of the pial blood vessels were excluded.

Statistical Analysis

Continuous variables, ordinal variables, and categorical variables were compared using the unpaired Student *t* test, Wilcoxon rank-sum test, and χ^2 test, respectively. First, we divided patients into 2 groups according to the presence or absence of CMBs to compare their clinical characteristics. Second, we assessed patients stratified by the presence and the location of CMBs (non-CMBs, strictly lobar CMBs, or any infratentorial, deep, or