Contribution of Deep Microbleeds to Stroke Recurrence: Differences between Patients with Past Deep Intracerebral Hemorrhages and Lacunar Infarctions

Toshio Imaizumi, MD, PhD, Shigeru Inamura, MD, and Tatsufumi Nomura, MD, PhD

Background: This study investigated the contribution of deep cerebral microbleeds (MBs) to stroke recurrences in patients with histories of deep intracerebral hemorrhages (ICHs) or lacunar infarctions (LIs). *Methods:* We prospectively analyzed stroke recurrences in patients admitted to our hospital who were treated for deep ICHs or LIs between April 2004 and December 2011. The number of deep MBs was counted on admission. Stroke recurrence–free rate curves were generated with the Kaplan–Meier method using the log-rank test. The odds ratios (ORs) for recurrent strokes were derived using multivariate logistic regression models, based on deep MBs and risk factors. *Results:* We evaluated magnetic resonance images or the recurrences of 231 deep-ICH patients (92 women, 68.0 ± 12.0 years old) and 309 LI patients (140 women, 70.7 ± 11.7 years old). The incidences of deep ICHs (1.5%/year) and LIs (2.1%/year) presenting as stroke recurrences were significantly larger in LI patients with deep MBs than in those without (.01 [P = .0001] and .08%/year [P = .005], respectively). However, there was no significant difference between deep-ICH patients with and without MBs in terms of incidence of recurrences. Multivariate analyses revealed that deep MBs independently and significantly elevated the rate of deep ICHs (OR, 19.0; P = .007) or LIs (OR, 3.62; P = .008) presenting as recurrences in LI patients, but not in deep-ICH patients, when adjusted for stroke risk factors. *Conclusions:* There may be differences between patients with deep ICHs and those with LIs in terms of the contribution of deep MBs to stroke recurrence. **Key Words:** Cerebral microbleeds—intracerebral hemorrhage—lacunar infarction—recurrence—risk factor.

Cerebral microbleeds (MBs) have been the focus of numerous investigations since their discovery 2 decades ago. Recent investigations have demonstrated an association between MBs and dementia, including Alzheimer disease (AD)[1,2] and vascular dementia.[3,4] AD was found to be associated with amyloid angiopathy, and amyloid concentrations were increased at lobar MB sites and declined with increasing distances from the MBs.[5] Cerebrospinal fluid markers of AD were associated with multiple MBs in patients with AD.[2] In healthy people without a history of stroke, mild cognitive impairment was associated with deep MBs.[3] Furthermore, MBs have been found to be associated with higher incidences of stroke recurrence, new disabilities, and poststroke depression.[6-14]

From the Department of Neurosurgery, Kushiro City General Hospital, Kushiro, Hokkaido, Japan.

Received November 6, 2014; revision received April 9, 2015; accepted April 17, 2015.

The authors declare that they have no financial conflicts of interest and they did not receive any grants.

Address correspondence to Toshio Imaizumi, MD, PhD, Department of Neurosurgery, Kushiro City General Hospital, 1-12 Shunkodai, Kushiro, Hokkaido 085-0822, Japan. E-mail: timaizum@d9.dion.ne.jp; kh8018@kushiro-cghp.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.04.027

Even in healthy individuals, MBs are risk factors for strokes, particularly intracerebral hemorrhages (ICHs).

Deep ICHs, lacunar infarctions (LIs), and deep MBs are thought to originate from similar types of damage to perforating arteries, including hypertensive microangiopathy and lipohialinosis. Pathologically, MBs on T2*-weighted (T2*-w) magnetic resonance images (MRIs) demonstrate hemosiderin in macrophages after microhemorrhages.[15,16] In Asian individuals, MBs were found to be more commonly associated with ICHs than cerebral infarctions.[17,18] However, little is known about the relationship between deep MBs and types of recurrent strokes in patients with small-vessel diseases. We hypothesized that there might be no differences between patients with histories of deep ICHs and LIs in terms of types of recurrent strokes associated with deep MBs. In this study, to identify the types of recurrent strokes associated with deep MBs in patients with histories of deep ICHs or LIs, we evaluated stroke recurrences in patients with histories of deep ICHs or LIs.

Subjects and Methods

Subjects

From April 2004 to December 2011, we enrolled patients consecutively admitted to our hospital within 7 days of experiencing deep ICHs or LIs (index strokes). Follow-up took place until March 2014 at the latest, and stroke recurrences were evaluated in all patients. We excluded patients with follow-up durations of less than 1 week, and those with unclear findings on MRIs due to motion or metal artifacts. All study procedures were approved by the Ethics Committee of Kushiro City General Hospital (IRB 2004-1).

Radiological Examinations

At least 2 physicians with Japanese Board Certifications in Neurosurgery and in Stroke diagnosed stroke types based on radiological findings. Imaging findings were reviewed by at least 1 physician without knowledge of clinical information or treatment assignment. Patients lacking neuroradiological findings related to index strokes on computed tomography and MRI were excluded from this study.

The severity of white matter hyperintensity (WMH) or periventricular hyperintensity (PVH) on fluid attenuated inversion recovery imaging was rated according to the Fazekas scale (WMH: grade (Gr) 1, punctuate; Gr 2, early confluence; and Gr 3, confluent; and PVH: Gr 1, caps or lining; Gr 2, bands; and Gr 3, irregular extension into the deep white matter).[19] In this study, white matter lesions (WMLs) of Fazekas grade 3 for WMH and/or PVH were regarded as WML Gr 3. WML of 3 > grades = 2 for WMH and/or PVH were regarded as WML Gr 2. Finally, WML of 2 > grades = 1 for WMH and/or PVH were regarded as WML Gr 1. Neither WMH nor PVH was regarded as WML Gr 0. Dot-like, low-intensity spots on T2*-w MRI with diameters less than 10 mm were defined as MBs. The locations of MBs were grouped according to brain area according to the Microbleed Anatomical Rating Scale.[20] Deep areas included the territories of the perforating arteries and the infratentorial regions (brain stem and cerebellum). Lobar areas included subcortical and cortical areas in this study.

Patients' medications were recorded when stroke recurrences occurred, when repeat MRIs were performed in patients without recurrence around 1 year after the onset of index strokes, or when final medical examinations were performed in cases with less than 1 year of follow-up after index stroke onset. Fasting blood samples were obtained the morning after initial admission. Diabetes mellitus was defined according to the National Diabetes Data Group diagnostic criteria. In terms of smoking history, patients were categorized into "cigarette smoking" or "nonsmoking" groups on admission; the latter included regular cigarette smokers who quit 1 year earlier. Habitual alcohol intake was defined as alcohol consumption exceeding 100-g ethanol per week. Subjects were considered hypertensive if their blood pressure repeatedly exceeded 140/85 mm Hg or if they were taking antihypertensive medications. At each follow-up visit, antihypertensive drug therapies were titrated to achieve a target blood pressure of 140/85 mm Hg. The methods and diagnostic approach used in this study were described in detail in our previous articles.[11,12]

Statistics

To investigate the relationship between deep MBs and stroke recurrences, patients were divided into subgroups based on the number of MBs or antiplatelet drug use. We generated recurrence-free rate curves by the Kaplan–Meier method. Stroke recurrence rates were compared by the log-rank test. Overall frequencies of categorical variables were calculated in the form of odds ratios (ORs) and 95% confidence intervals (CIs) from univariate logistic regression analyses. Multivariate analyses were also performed using the regression model. Where applicable, 95% CIs were calculated for the estimated ORs. A P value of less than .05 was considered statistically significant.

Results

Patients with Lacunar Infarctions as Index Strokes (LI Patients)

We consecutively enrolled 337 LI patients during the study period. Twenty-eight patients were excluded, including 6 with pacemakers, 7 who died within 7 days after the index stroke onset, 5 with unclear findings on