The Severity of White Matter Lesions Possibly Influences Stroke Recurrence in Patients with Histories of Lacunar Infarctions

Toshio Imaizumi, MD, PhD, Shigeru Inamura, MD, Tatsufumi Nomura, MD, PhD, Aya Kanno, MD, and Sang Nyon Kim, MD, PhD

Background: To investigate the recurrent stroke types associated with white matter lesions (WMLs), we prospectively observed recurrences in patients with histories of lacunar infarctions (LIs). *Methods:* We prospectively analyzed the types of stroke recurrences in 305 patients (138 women, 70.2 ± 11.7 years old) consecutively admitted to our hospital with LIs from April 2004 to December 2011. WMLs were graded using Fazekas' grades (Gr). Recurrence-free rate curves were generated by the Kaplan–Meier method using the log-rank test. *Results:* The follow-up period was 50.7 ± 32.8 (.25-114) months. During this period, 62 strokes recurred. The incidences of strokes (all types), LIs, and deep intracerebral hemorrhages (ICHs) presenting as recurrences in 112 patients with Gr 2-3 were 6.2, 2.0, and 1.5 %/year, respectively, values that were significantly greater than those seen in 79 patients with Gr 0 (2.1 [P = .0001], .6 [P = .014], and .5 %/year [P = .016], respectively), and in 114 patients with Gr 1 (2.8 [P = .003], .9 [P = .009], and .6 %/year [P = .043], respectively). There was no significant difference among Gr 0, 1, and 2-3 in incidences of recurrences presenting as lobar ICHs, atherothrombotic infarctions, or cardioembolic infarctions. Multivariate analyses demonstrated that Gr 2-3 significantly and independently elevated the rate of deep ICHs or LIs presenting as recurrences after adjustment for risk factors. *Conclusions:* The presence of high-grade WMLs elevated the rate of stroke recurrences presenting as LIs and deep ICHs, but not other types. **Key Words:** White matter lesions—stroke recurrences—lacunar infarction—intracerebral hemorrhage—cerebral microbleeds.

White matter lesions (WMLs) are correlated with dementia, including Alzheimer's disease and cerebrovascular dementia.[1-3] In patients experiencing Alzheimer's disease, amyloid angiopathy induces WMLs and hippocampal atrophy.[4,5]

Furthermore, WMLs are an independent predictor of clinical outcome after ischemic stroke,[6] as well as risk of symptomatic stroke,[7] stroke recurrence,[8,9] and hemorrhagic transformation after thrombolysis for ischemic stroke,[10] and WMLs may also be surrogate markers of severe microangiopathy. Numerous prior investigations demonstrated that deep and lobar microbleeds (MBs) were significantly related to WMLs,[11-14] suggesting that both MBs and WML originated from cerebral microangiopathies, including hypertensive microangiopathy and amyloid angiopathy. MBs are scars of microhemorrhages, whereas WMLs are chronic ischemic lesions. In addition to microangiopathies, WMLs are possibly related to collateral flow.[15]

WMLs are commonly observed in elderly persons, even those without a history of stroke or cognitive disorders, suggesting that low-grade WMLs may be a normal finding. Nonetheless, it is unclear whether these findings

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

Received April 5, 2015; revision received May 19, 2015; accepted May 26, 2015.

The authors have no relevant financial interests and did not receive any grants.

The authors have nothing to disclose.

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.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.05.023

provide useful clinical information regarding therapy. WMLs correlate with strokes related to microangiopathies, particularly lacunar infarctions (LIs) and intracerebral hemorrhages (ICHs).[8,12,13,16] Although WMLs are associated with microangiopathies, little is known about the types of recurrent strokes they are associated with. To investigate this issue, we prospectively observed stroke recurrences in patients with histories of LIs.

Subjects and Methods

Subjects

From April 2004 to December 2011, we enrolled patients who were consecutively admitted to our hospital within 7 days of experiencing LIs (index strokes). Follow-up took place until March 2014, 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 magnetic resonance (MR) images owing 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 who was blind to both clinical information and treatment assignment. Patients lacking neuroradiological findings related to LIs as index strokes on computed tomography and MR imaging (MRI) were excluded from this study.

The severities of white matter hyperintensity (WMH) and periventricular hyperintensity (PVH) on fluid-attenuated inversion recovery imaging were 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).[17] In this study, WMLs of Fazekas Gr 3 for WMH and/or PVH were regarded as WML Gr 3. WMLs of 3 > Gr = 2 for WMH and/or PVH were regarded as WML Gr 2. Finally, WMLs of 2 > Gr = 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*-weighted MRI with diameters less than10 mm were defined as MBs. The locations of MBs were grouped according to brain area according to the Microbleed Anatomical Rating Scale.[18] Deep areas included the territories of the perforating arteries and the infratentorial regions (brain stem and cerebellum).

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.[12,13]

Statistics

To investigate the relationship between WML Gr and stroke recurrence, patients were divided into subgroups based on Gr. We generated recurrence-free rate curves by the Kaplan–Meier method. Stroke recurrence rates were compared by the log-rank test. Discrete variables are presented as count and percentage (%), and continuous variables are shown as mean and standard deviation. To perform comparisons between groups, we used the Student t test (parametric data) and Mann–Whitney U test (nonparametric data). Overall frequencies of categorical variables were calculated in the form of odds ratios (ORs) and 95% confidence intervals (CIs) derived from univariate logistic regression analyses. To examine the risk factors for recurrences, multivariate logistic regression analyses were performed using the types of recurrent strokes as the dependent variables. Where applicable, 95% CIs were calculated for the estimated ORs. A P value of less than .05 was considered statistically significant.

Results

We consecutively enrolled 337 LI patients during the study period. Thirty-two patients were excluded, including 6 with pacemakers, 7 who died within 7 days after stroke onset, 8 with unclear findings on MRI, and 11 with insufficient records. Thus, 305 of the initial 337 LI patients were followed and stroke recurrences were investigated. The 305 patients were divided into 3 groups based on WML Gr 0, 1, and 2-3. Table 1 presents stroke-related variables in the 3 groups.

Univariate analyses demonstrated significant differences between patients with Gr 0 and Gr 2-3, and between Gr 1 and Gr 2-3, in variables including age 65 years or older, smoking, deep MBs, and lobar MBs (Table 1).

Stroke recurrence–free rate curves, generated by the Kaplan–Meier method, demonstrated that the incidences