Nascent Deep Microbleeds and Stroke Recurrences

Toshio Imaizumi, MD, PhD, Shigeru Inamura, MD, Ikuhide Kohama, MD, PhD, Kazuhisa Yoshifuji, MD, PhD, Tatsufumi Nomura, MD, PhD, and Katsuya Komatsu, MD, PhD

Background: Cerebral microbleeds (MBs) on gradient echo T_2*-weighted magnetic resonance imaging (MRI) scans are associated with the severity of cerebral microangiopathies. This study investigated the contributions of nascent deep MBs to stroke recurrence. *Methods:* We prospectively analyzed nascent deep MBs in patients admitted to our hospital who were treated for index strokes between April 2004 and November 2009. The number of nascent deep MBs was counted on T_2*-weighted MRI scans around 1 year after the index strokes, and compared to previous MRIs on admission. Stroke recurrence–free rate curves were generated using the Kaplan–Meier method using the log-rank test. The odds ratio for nascent deep MBs was derived using a multivariate logistic regression model that was based on recurrent strokes and other risk factors. *Results:* We evaluated the MRIs (interval between MRIs 14.6 ± 5.9 months) of 508 patients (207 women; 68.9 ± 11.5 years), with a follow-up period of 44.1 ± 15.4 months. Repeated T_2*-weighted MRI scans revealed 256 nascent deep MBs in 116 of 508 patients. The incidence of deep intracerebral hemorrhage was significantly greater in patients with nascent deep MBs than those without (2.0% *vs* 0.4% per year, respectively; $P < .0001$). Multivariate analyses revealed that the rate of nascent deep MBs was significantly elevated in patients whose stroke recurrences took the form of deep intracerebral hemorrhages (odds ratio 5.41; $P = .007$), when adjusted for hypertension, preexisting MBs, and other risk factors. *Conclusions:* Our findings suggested that nascent deep MBs might be associated with stroke recurrence, in particular with deep intracerebral hemorrhage. **Key Words:** Cerebral microbleeds—intracerebral hemorrhage—stroke—recurrence—risk factor.

Cerebral microbleeds (MBs) have been considered to be surrogate markers for stroke recurrences,[1-3] prognoses in stroke patients,[4,5] and dementia.[6,7] Recently, Bokura et al[8] reported that MBs are also risk factors for strokes, in particular intracerebral hemorrhages (ICHs), even in healthy individuals. Greater numbers of MBs have been found to be associated with higher incidences of stroke recurrence, including lacunar infarctions and ICHs,[2,5,9] suggesting that increased MB counts might be related to advanced microangiopathies of the cerebrum.

Nascent or disappearing MBs have occasionally been observed on gradient echo T_2*-weighted magnetic resonance imaging (MRI) scans in patients with strokes.[10-13] Pathologically, MBs on T_2*-weighted MRIs were hemosiderin in macrophages after microhemorrhages.[14] The number of MBs possibly depends on hemosiderin absorption after microhemorrhage and the occurrence of nascent microhemorrhages. Some MBs remain visible on T_2*-weighted MRIs for several years.[12] Moreover, the duration of MB visibility may vary with hemosiderin absorption, MRI parameters, and/or MRI magnetic field strength.[13,15-17]

We hypothesized that the stage of advanced microangiopathy might be related to the appearance of nascent MBs, according to stroke recurrence. However, little is

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

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

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known about the relationship between nascent MBs and recurrent strokes. In addition, histopathologic and clinical examination has revealed differences between deep and lobar MBs.[18,19] In this study, to identify the types of recurrent strokes and other factors associated with nascent deep MBs, we prospectively examined these MBs in patients experiencing stroke recurrences.

Methods

Subjects

Between April 2004 and October 2009, we enrolled patients who were consecutively admitted to our hospital within 7 days of experiencing a stroke (index stroke). Follow-up took place until January 2010 at the latest, and stroke recurrences were evaluated in all patients. For patients with long follow-up periods, repeat MRI scans were performed around 1 year after the index strokes and were compared to the initial MRI scan obtained at admission to identify any nascent MBs and any asymptomatic lesions, including ICHs and infarctions. In this study, "asymptomatic" lesions were defined as those "without focal signs." We excluded patients without follow-up MRI scans around 1 year after index strokes or patients with a modified Rankin Scale score ≥4, and patients with unclear findings on MRI scans because of motion or metal artefacts. All study procedures were approved by the Ethics Committee of Kushiro City General Hospital.

Radiologic Examination

More than 2 physicians with Japanese Board Certifications in Neurosurgery and Stroke diagnosed the stroke type based on radiologic findings. Imaging findings were reviewed by >1 physician without knowledge of clinical information or treatment assignment. We divided strokes into 3 subtypes: ICH (lobar and deep ICH), subarachnoid hemorrhage, and cerebral infarction (i.e., lacunar infarction, atherothrombotic infarction, cardioembolic infarction, and infarction of unknown origin). All strokes were verified by computed tomographic (CT) and MRI scans on admission. To differentiate stroke types, we performed magnetic resonance angiographies and obtained MRIs using the following sequences: gradient echo T_2*-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). In addition to CT and MRI scans, stroke subtypes were determined by electrocardiogram (including Holter electrocardiogram), echocardiogram, and/or digital subtraction angiography. Strokes were diagnosed according to neurologic findings on MRI and CT scans. Patients with neurologic deficits, including transient neurologic deficits, and those lacking neuroradiologic findings on CT and MRI scans were excluded from this study. Lacunar infarctions (≤15 mm in diameter) in the territories of the perforating arteries were verified by MRI, particularly DWI, on admission or 1 day after admission. Small infarctions associated with emboli related to atrial fibrillation were diagnosed as cardioembolic infarctions, while small infarctions related to stenoses of the main cerebral arteries were diagnosed as atherothrombotic infarctions. ICHs associated with head trauma were excluded from this study.

Dot-like, low-intensity spots on T_2*-weighted MRI with diameters <10 mm were defined as MBs. Low-intensity spots with diameters <1 mm were excluded. Low-intensity spots without focal signs and with diameters ≥10 mm were classified as definite asymptomatic ICHs. The absence of calcifications was confirmed by CT scan. All MBs were observed and recorded on admission, excluding MBs in areas surrounding the ICH and within the globus pallidus. Identical slices of the T_2*-weighted MRIs could not be guaranteed, but we simultaneously investigated the MBs in the upper and lower slices to compare their condition and number. We carefully created the second radiographs in same manner using the same 1.5-T scanner (GE Signa Exicite1.5 T, USA) and the same developer. Nascent MBs means new MBs have appeared by the time of the second T_2*-weighted MRI, while a disappeared MB means that previous MBs have already disappeared. The locations of MBs were grouped according to brain area according to the Microbleed Anatomical Rating Scale (MARS),[20] and MBs were divided into 2 subgroups: those in lobar areas and those in deep areas. Deep areas included the territories of the perforating arteries and the infratentorial regions (brain stem and cerebellum). The severity of white matter hyperintensity (WMH) or periventricular WMH (PVH) on FLAIR imaging was rated according to the Fazekas scale (WMH: grade 1 punctuate, grade 2 early confluence, and grade 3 confluent; PVH: grade 1 caps or lining, grade 2 bands, and grade 3 irregular extension into the deep white matter).[21] Grades ≥2 of WMH or/and PVH in the Fazekas scale were regarded as severe white matter lesions (WMLs). The locations of ICHs were also divided in the same manner. T_2*-weighted, FLAIR, and DWI MRI sequences, acquired using a 1.5-T scanner, were obtained in the axial plane with the following parameters: 450/26/2, 8800/141/1, and 5000/84/2 (TR/TE/excitations), respectively; a flip angle of 20°; a section thickness of 6.5 mm with a gap of 1.0 mm; and a matrix size of 256 × 205.

Variables

Fasting blood samples were obtained the morning after initial admission. Diabetes mellitus was defined according to the National Diabetes Data Group diagnostic criteria.[22] 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