Asymptomatic microbleeds in moyamoya disease: $T_2^*$-weighted gradient-echo magnetic resonance imaging study

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Object. The aim of this study was to investigate the incidence of asymptomatic microbleeds (MBs) in patients with moyamoya disease (MMD) by using a 3-tesla magnetic resonance (MR) imaging unit.

Methods. Data on 63 patients hospitalized with MMD between 1999 and 2004 were retrospectively examined to determine the incidence of asymptomatic MBs. Gradient-echo $T_2^*$-weighted MR imaging studies obtained using 3- and 1.5-tesla units were available in 25 patients. These patients consisted of five men and 20 women, ranging in age from 17 to 66 years (mean age 41 ± 14 years). Ischemic MMD was diagnosed in 18 patients, and hemorrhagic MMD in seven. The incidence of MBs was also evaluated using the same 3-tesla MR imaging unit in 34 healthy volunteers including seven men and 27 women, ranging in age from 18 to 71 years (mean age 33 ± 12 years). Using the 3-tesla MR unit, asymptomatic MBs were demonstrated in seven patients (28%) by using the 1.5-tesla unit. In the 3-tesla MR studies in healthy individuals, MBs were found in two patients (5.8%). Based on 3-tesla MR studies, the incidence of MBs was significantly higher in patients with MMD compared with that in healthy individuals. Asymptomatic MBs were demonstrated in eight (44%) of 18 patients with ischemic MMD and three (43%) of seven patients with hemorrhagic MMD.

Conclusions. Microbleeds are significantly more common in patients with MMD than in healthy individuals regardless of the disease type. The evaluation of MBs with $T_2^*$-weighted 3-tesla MR imaging might contribute to the treatment of MMD.

Key Words • moyamoya disease • microbleed • $T_2^*$-weighted magnetic resonance imaging

MOYAMOYA disease has been considered a progressive stenoocclusive disease at the terminal portion of bilateral internal carotid arteries, with moyamoya vessels developing as collateral channels.4 This disease entity has been classified roughly into two types according to clinical features: ischemic MMD and hemorrhagic MMD. The former type is characterized by the onset of transient ischemic attack or cerebral infarction. In such cases, SPECT scanning usually reveals decreased rCBF.5 The latter type is distinguished by the onset of intracranial hemorrhage, which is usually confirmed on CT scanning.6 Ischemic MMD usually occurs in pediatric patients, whereas almost half of the hemorrhagic MMD cases occur in adults.7 Although surgical revascularization has been thought to be beneficial in patients with ischemic MMD, the efficacy of the procedure remains equivocal in patients with hemorrhagic MMD. Determining the type of MMD from which a patient suffers is crucial in the treatment of the disease.8

Gradient-echo $T_2^*$-weighted MR imaging is extremely sensitive in detecting small remains of previously asymptomatic cerebral MBs.6,15 Previous histopathological reports have shown that these small areas of signal loss are correlated with perivascular hemosiderin deposition around angiopathic arterioles.9 Microbleeds are frequently detected in patients with lacunar infarction as well as in those with primary ICH and even in a small number of healthy individuals, usually in the corticospinalcortical regions and the basal ganglia/thalami.8,14 Microbleeds may be seen as general markers of various types of bleeding-prone cerebral microangiopathy or vascular vulnerability.14 In this paper, we attempted to provide information pertaining to asymptomatic MBs in patients with MMD based on a retrospective analysis of MR imaging studies.

Clinical Material and Methods

Patient Population
Between 1999 and 2004, 63 patients with MMD were ad-
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mitted to our clinic. The MMD was diagnosed using cerebral angiography studies, according to the diagnostic criteria updated in 1997. Based on clinical and radiological findings, 55 patients had a diagnosis of ischemic MMD, and eight hemorrhagic MMD. Routine radiological evaluation of MMD has been performed using CT and SPECT scanning and 1.5-tesla MR imaging without T$_2^*$-weighted gradient-echo images. Eighty-four revascularization surgeries were performed in 57 patients between 1999 and 2004, and 23 surgeries were performed before 1999.

Since November 2003, T$_2^*$-weighted gradient-echo images acquired using 3- and 1.5-tesla MR units were available in 25 patients who had been admitted to our clinic or were outpatients. These patients consisted of five men and 20 women, ranging in age from 17 to 66 years (mean age 41 ± 14 years). Ischemic MMD was diagnosed in 18 patients, and hemorrhagic MMD in seven. Among the 18 patients with ischemic MMD, three were men and 15 were women, with a mean age of 40 ± 14 years. Five of the 18 patients underwent the MR imaging studies before revascularization surgery, and the remaining 13 underwent imaging after revascularization. Five of these 13 patients experienced delayed symptomatic hemorrhage after surgery and before MR imaging. In the seven patients with hemorrhagic MMD, two were men and five were women, with a mean age of 40 ± 17 years. Four of these seven patients underwent MR imaging before surgery and three after surgery. No patients among those with hemorrhagic MMD experienced recurrent hemorrhage either before or after surgery. In total, nine patients underwent MR imaging before revascularization and 16 patients underwent imaging after surgery (Table 1).

Among the 25 patients, 11 were receiving antiplatelet drug therapy at the time of MR imaging. Six patients had never received antiplatelet therapy and the remaining eight patients each had a history of antiplatelet therapy but had discontinued it more than 1 year before MR imaging. Patients with cerebral aneurysms confirmed on angiography were excluded from this study, and no patient was studied within 24 hours after angiography.

The incidence of MBs in 34 healthy volunteers was also studied using the same 3-tesla MR unit. These seven men and 27 women ranged in age from 18 to 71 years (mean age 33 ± 12 years; Table 2).

Magnetic Resonance Images

All patients underwent imaging studies with the same 3-tesla MR unit (Magnetom Trio; Siemens, Enlargen, Germany). Axial T$_2^*$-weighted gradient-echo sequences were obtained (TR 612 msec; TE 18 msec; flip angle 20°; matrix 256 × 224; FOV 22 cm; slices 19; slice thickness 5 mm; and interslice gap 1.5 mm). At the same time, axial T$_1^*$-weighted turbo–spin echo sequences (TR 8400 msec; TE 108 msec; flip angle 150°; matrix 512 × 448; FOV 22 cm; slices 40; slice thickness 2.3 mm; and interslice gap 0.7 mm) and axial T$_1^*$-weighted three-dimensional MPRAGE sequences (TR 2000 msec; TE 4.4 msec; flip angle 8°; matrix 256 × 224; FOV 24 cm; slices 208; and slice thickness 1 mm) were acquired to distinguish MBs from the signal voids of cerebral arteries and from other mass lesions with hemorrhage such as cavernous angiomas.

During the 1.5-tesla MR imaging study, axial T$_2^*$-weighted gradient-echo sequences (TR 700 msec; TE 17 msec; flip angle 20°; matrix 256 × 168; section thickness 5 mm; and interslice gap 1 mm) were obtained using the same MR unit (Magnetom Symphony; Siemens). All images were reviewed by a single investigator (K.K.). Hypointense lesions representing MBs on the T$_2^*$-weighted images were defined as small hypointense areas (< 10 mm in diameter) with well-defined margins. Asymptomatic MBs in patients with hemorrhagic MMD were defined as hypointense lesions demonstrated in the region separate from where hemorrhages existed on CT scanning at hemorrhagic onset.

Statistical Analysis

Data on the incidence of MBs were statistically evaluated using the chi-square test or the Fisher exact test. Differences were defined as significant at a probability level less than 0.05.

Results

Incidence of MBs on 3-Tesla Imaging Studies

Among the 25 patients with MMD, asymptomatic MBs were found in 11 (44%), that is, in eight (44%) of 18 patients with ischemic MMD and three (43%) of seven patients with hemorrhagic MMD. No significant difference was observed in the incidence of MBs between the two groups according to statistical analysis with the chi-square test (p = 0.94). Asymptomatic MBs were demonstrated in five (56%) of the nine patients who had undergone MR imaging before revascularization surgery and in six (38%) of the 16 patients who had undergone imaging after surgery (Table 1). In the 18 patients with ischemic MMD, 13 underwent MR imaging after revascularization. Five of these 13 patients experienced delayed symptomatic hemorrhage following surgery. Among patients with ischemic MMD, it was calculated that three (60%) of the five patients with postoperative delayed hemorrhage had asymptomatic MBs and two (25%) of the eight patients without had asymptomatic MBs. In the patients with hemorrhagic MMD, asymptomatic MBs occurred in two of four patients who had un-
dergone imaging before surgery and in one of three patients who had undergone imaging after surgery.

As for the number of asymptomatic MBs, one was found in six patients, two in three patients, and three or more in two patients. Microbleeds were predominantly located in the periventricular white matter (Cases 5 and 7–11). Magnetic resonance images demonstrating MBs and information about the 11 patients with these lesions are shown in Fig. 1.

Asymptomatic MBs were detected in five (45%) of the 11 patients on antiplatelet therapy, three (33%) of the six patients with no history of antiplatelet therapy, and four (50%) of the eight patients with a history of antiplatelet therapy. There was no significant difference in the incidence of MBs among these three groups according to statistical analysis with the chi-square test.

**Illustrative Case: Case 5**

This 49-year-old man presenting with recurrent transient attacks of left hemiparesis and left hemipaesthesia was admitted to our clinic in April 2004. An $^{123}$I-IMP SPECT study revealed decreased rCBF in the bilateral frontal lobes (Fig. 2A). Results of FLAIR imaging with a 1.5-tesla MR unit demonstrated ischemic lesions in the deep white matter of the bilateral frontal lobes (Fig. 2B). No hemorrhagic lesion was revealed on CT scanning (Fig. 2C). According to the clinical symptoms and routine radiological studies, ischemic MMD was diagnosed. Nonetheless, $T_1$-weighted imaging with a 3-tesla MR unit clearly revealed multiple MBs in the periventricular regions (Fig. 2D).

**Incidence of MBs in Healthy Individuals**

Asymptomatic MBs were demonstrated in two (5.8%) of 34 healthy volunteers examined using a 3-tesla MR unit (Table 2). One volunteer was a 55-year-old woman with an asymptomatic MB in the right caudoputamen. The other volunteer was a 26-year-old woman with an MB in the right occipital lobe. In the latter case the lesion was demonstrat-
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**Fig. 2.** Case 5. A: An $^{123}$I-IMP SPECT scan revealing decreased CBF in the bilateral frontal lobes. B: A FLAIR 1.5-tesla MR image demonstrating mild ischemic lesions in the deep white matter of the frontal lobes. C: A CT scan displaying no hemorrhagic lesion. D: A $T_2^*$-weighted 3-tesla MR image revealing multiple MBs in the periventricular regions.

**Fig. 3.** A $T_2^*$-weighted 3-tesla image (A) and $T_2$-weighted images (B and C) obtained in a 26-year-old healthy female volunteer. The former image demonstrates an MB (arrow) in the right occipital lobe, which was described as a heterogeneous intensity mass on $T_2$-weighted imaging, indicating that the lesion can be diagnosed as cavernous angioma. Note that C is a magnified version of the image in B.

ed as a heterogeneous mass on MPRAGE imaging and was diagnosed as incidental cavernous angioma (Fig. 3A and B). The incidence of MBs in the 3-tesla MR study was significantly higher in the patients with MMD than in healthy individuals ($p = 0.0005$, chi-square test).

**Comparison of Sensitivity in Detecting MBs Between 3- and 1.5-Tesla MR Units**

Whereas asymptomatic MBs were found in 11 (44%) of 25 patients in the 3-tesla study, these lesions could be detected in only seven (28%) of 25 patients in the 1.5-tesla study (Table 2). The quality of the images obtained using the 3-tesla unit was greater than that of the images acquired with the 1.5-tesla unit. For example, an asymptomatic MB was demonstrated clearly on the 3-tesla study in Cases 3 and 8 but not on the 1.5-tesla study (Fig. 4). Nonetheless, there was no statistically significant difference in sensitivity between the two MR units in this study ($p = 0.239$, chi-square test).

**Discussion**

**Effectiveness of the 3-Tesla MR Unit in Detecting Asymptomatic MBs in Patients With MMD**

Cerebral MBs were detected using gradient-echo $T_2^*$-weighted MR imaging in 51 to 80% of patients with primary ICH, in 20 to 36% of patients with ischemic stroke, in 32% of patients with Alzheimer disease, and in 31 to 69% of patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Therefore, MBs can be thought of as general markers of various types of bleeding-prone cerebral angiopathy.

In the 3-tesla MR study, the incidence of asymptomatic MBs in patients with MMD, with ischemic MMD, and with hemorrhagic MMD was 44, 44, and 43%, respectively. There was no significant difference in the incidence of MBs between the two MMD onset types. As for the incidence in healthy individuals in the 3-tesla study, MBs were found in only 5.8%, a rate not so different from the MB incidence in healthy individuals in previous 1.5-tesla studies. The incidence of asymptomatic MBs in patients in the 3-tesla study was significantly higher than that in healthy individuals regardless of the MMD onset type.

Data from previous autopsy studies have revealed that ruptured or dilated vessels with diminution of the elastic lamina, stenotic vessels with wall thickening, and vessels along with microaneurysm formation could be observed simultaneously in a patient with MMD. Our data indicate that ischemic and hemorrhagic lesions can coexist in the same patient with MMD. These findings might suggest that MB occurs with equal probability regardless of the MMD onset type.

Microbleeds were observed predominantly in the periventricular deep white matter in patients with MMD, al-
though they were usually found in corticosubcortical regions or the basal ganglia/thalami in patients with other pathological conditions.\textsuperscript{8,14} These observations are compatible with the fact that intraventricular hemorrhage is common in patients with hemorrhagic MMD associated with an increased hemodynamic load in the vessels supplying the walls of the ventricles or periventricular region, as previously reported.\textsuperscript{7}

Although most data in previous reports were obtained using 1.5-tesla MR units,\textsuperscript{1,2,5,8,10,11,13–16} we used a 3-tesla unit in the present study because images acquired with the higher-field MR imaging unit seem to have better resolution than those obtained with the lower field. Nonetheless, a comparison study in this small series could not reveal a significant difference in the sensitivity in detecting MBs between the two MR units.

Wong, et al.,\textsuperscript{17} reported that MBs were found more frequently in aspirin users with a history of ICH. At our institution, antiplatelet therapy is routinely indicated in patients with ischemic MMD until 6 to 12 months after revascularization surgery but not in patients with hemorrhagic MMD. Therefore, our series included at the time of MR imaging 11 patients on antiplatelet therapy, six with no history of antiplatelet therapy, and eight with a history of antiplatelet therapy. Although the incidence of MBs was relatively higher in patients currently on or with a history of antiplatelet therapy compared with patients with no history, there was no significant difference.

**Relationship Between the Incidence of MBs and Revascularization Surgery, and MBs as Potential Predictors of Subsequent Postoperative Hemorrhage in MMD**

Data in recent reports have revealed that the existence of MBs appears to be a potential risk factor for subsequent intracranial hemorrhage following ischemic stroke\textsuperscript{2,12} or for major symptomatic hemorrhage following intraarterial thrombolytic therapy.\textsuperscript{9} Fan, et al.,\textsuperscript{2} conducted a prospective analysis of 121 patients with acute cerebral infarction and reported that four (9.3\%) of 43 patients with MBs had ICH during the follow-up period of 27 months.

In our study, asymptomatic MBs were found in 56\% of the patients who underwent MR imaging before revascularization surgery and in 38\% of the patients who underwent imaging after surgery. Because it is unclear when MBs occurred in our series, the effects of revascularization surgery on the occurrence of MBs could not be evaluated. In the patients with ischemic MMD, MBs were found in 60\% of the patients with delayed hemorrhage after surgery and in 25\% of the patients without. Although these observations might indicate that MBs are a potential risk factor for hemorrhage following revascularization surgery in patients with ischemic MMD, a large cohort study is required to resolve this issue.

Given that there was no patient with hemorrhagic MMD who had experienced recurrent hemorrhage before MR imaging, the relationship between the presence of MBs and the probability of recurrent hemorrhage in patients with hemorrhagic MMD could not be evaluated. Currently, a cohort, randomized, controlled study of MMD in adults in Japan (JAM trial) is in progress to determine whether superficial temporal artery–middle cerebral artery anastomosis has prophylactic effects against recurrent hemorrhages in patients with hemorrhagic MMD.\textsuperscript{11} The evaluation of MBs combined with the aforementioned study would provide useful information on this issue.

**Conclusions**

Our data provide the first evidence that MBs can be found significantly more often in patients with MMD than in healthy individuals, regardless of the reason for MMD onset. Evaluation of MBs by using T\(_2^*\)-weighted 3-tesla MR imaging might contribute to the treatment of MMD.

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**References**


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