Spatial Relationship between Cerebral Microbleeds, Moyamoya Vessels, and Hematoma in Moyamoya Disease

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Background: Adult moyamoya disease (MMD) is known to have high incidence of cerebral microbleeds (cMBs); however, the clinical significance still remains unclear. We investigated the frequency of cMBs in a large number of patients and analyzed the patterns of MB distribution in association with the location of the hematoma and moyamoya vessels. *Methods:* We studied 259 consecutive patients with MMD using prospectively collected database. One hundred ninety-one patients were eligible for the present study, and image analysis was performed retrospectively. The presence of cMBs and remains of hemorrhage were determined using gradient-echo T2*-weighted sequence (1.5 T). The development of moyamoya vessels was assessed on source images of time-of-flight magnetic resonance angiography. The analysis consists of descriptive assessment of the spatial relationship between cMB, remains of hemorrhage, and moyamoya vessels. Statistical analysis was performed to calculate relative risk ratio in the presence of cMBs in relation to the remains of hemorrhage (macrohematoma), age of onset, and the presence of concomitant moyamoya vessels. *Results:* Thirty MBs were observed in 20 adult MMD patients (16.9%). MBs were located predominantly in the periventricular white matter (63.3%) followed by the basal ganglia/thalami (20%). Comparing the patients with cMBs from those without, hematoma was more frequently observed in patients with cMBs (odds ratio [OR] 4.29; 95% confidence interval [CI] 1.58-11.62; $P = .0062$). Patients with adult onset was more likely to demonstrate cMBs (14.4%) compared with the patients with pediatric onset (4.1%) (OR 3.93; 95% CI 1.11-13.91). Moyamoya vessels appeared in the lateral part of the trigon, and the periventricular white matter was significantly associated with the presence of cMBs (lateral part of the trigon; OR 3.29 [1.59-6.82], $P = .0019$, periventricle of the body of lateral ventricle; OR 2.40 [1.20-4.79], $P = .0214$, respectively). cMBs accompanied concomitant arteries in 23 (76.7%) lesions. The subependymal–leptomeningeal artery anastomosis was the most common pattern (n = 20, 66.7%). *Conclusions:* Spatial relationship was demonstrated between the moyamoya vessels and perivascular hemosiderin deposition particularly around the subependymal–leptomeningeal anastomosis, suggesting the mechanism for the development of cMBs in MMD. Present study further supports previous findings that cMBs potentially serve as a marker for the bleeding-prone microangiopathy in MMD. The significance of the present study lies in selecting optimal surgical candidate for preventing future hemorrhage by the presence of the cMBs, whereas current surgical indication relying on the degree

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of ischemia frequently fails to detect patients with future hemorrhage. **Key Words:** Moyamoya disease—microbleeds—intracranial hemorrhage—intraventricular hemorrhage—subependymal artery—medullary artery.

Introduction

MMD is a progressive steno-occlusive cerebrovascular disease that is characterized by the presence of net-like collateral vessels (moyamoya vessels) at the base of the brain.[1] Recent reports demonstrated that the incidence of cerebral microbleeds (cMBs) was higher in patients with MMD compared with healthy subjects.[2-6] In addition, the presence of cMBs predicts the future risk of hemorrhage.[2,7] These results suggest that cMBs can serve as a marker of bleeding-prone microangiopathy in MMD. A certain pattern of distribution of MBs serves to indicate microangiopathy developed by the different mechanisms. cMBs in the basal ganglia and cortical–subcortical distribution are characteristic in hypertensive lipohyalinosis and amyloid angiopathy, respectively. Similarly, it is speculated that MMD may demonstrate specific pattern of the distribution of cMBs and follow the spatial distribution of hematoma and moyamoya vessels. The investigations of these spatial relationships may further elucidate the clinical significance and the mechanism for the development of the cMBs in MMD.

In addition to the spatial distribution of cMBs, the exact number or locations of the bleeding have also not been fully evaluated previously. T2* gradient-echo or susceptibility weighted image not only demonstrate cMBs but also reveals remains of tiny intracerebral hemorrhage throughout life, which enables determining the cause of the hemorrhage years after the bleeding event. This is particularly useful to determine the location of the hemorrhage in primary intraventricular hemorrhage, a frequent manifestation of the intracranial bleeding in adult MMD. Furthermore, the source image of magnetic resonance angiography (MRA) demonstrates the enlarged basal perforators and choroidal arteries developed as a collateral circulation, which potentially reveal spatial association between the moyamoya vessels and the cMBs. Present study attempted to provide additional information by performing an analysis of the frequency and distribution patterns of MBs in association with the hematoma location and moyamoya vessels in a large consecutive series of patients with MMD.

Patients and Methods

We examined 259 consecutive patients with MMD at the Department of Neurosurgery of the Hokkaido University Hospital from March 1980 to March 2012. The diagnosis was based on the guidelines established by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan.[8] These patients were referred to our hospital for the diagnosis and the treatment. Demographic information, including history of stroke, medical history, and medications for hypertension, diabetes mellitus, or hyperlipidemia, was collected. We also recorded the prevalence of antithrombotic therapy before the occurrence of recurrent stroke in each patient. Their information is tabulated in the database prospectively and used in this study to select eligible patients in this study.

Since 2003, a standardized magnetic resonance imaging (MRI) protocol has been employed for all the time points that include fluid-attenuated inversion recovery (FLAIR), T2, and gradient recalled echo (GRE) sequences and MRA.[5] Gradient-echo T2*-weighted sequence was available for assessment in 191 patients (73.7%; 56 men and 135 women; age, 2-86 years; mean age, 40.0 + 19.3 years). One hundred forty-one of the 191 patients underwent revascularization surgery (73.8%). In turn, 70 of these 141 patients underwent gradient-echo T2*-weighted sequence studies before revascularization surgery, and the remaining 71 underwent imaging after revascularization surgery. No patient had a known pathogenesis, such as head trauma, cerebral amyloid angiopathy, current anticoagulant therapy, arteriovenous malformation, cavernoma, or other systemic coagulation disorder.

Imaging Analysis

MRI was performed every 1 year and/or at the time of recurrent stroke using a 1.5 T MR scanner (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany).

The imaging protocol consisted of the axial spin-echo T1-weighted imaging (WI) (repetition time/echo time [TR/TE] = 600/14 ms, number of excitation [NEX] = 1, matrix size = 512 × 512), axial fast spin-echo T2WI (TR/TE = 4000/96 ms, effective echo train length = 7, NEX = 1, matrix size = 512 × 512), and axial gradient-recalled echo T2*WI (TR/TE = 800/26 ms, flip angle = 20°, NEX = 1, matrix size = 256 × 256). All images were acquired with a 240-mm field of view, a 5.0-mm section thickness, and a 1.5-mm intersection gap.

Axial source images acquired by the 3-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) (TR/TE = 27/7.2 ms; flip angle = 20°; NEX = 1, field of view = 230 mm; recon matrix = 512 × 512; number of slabs = 4 [180 sections]; section thickness = .65 mm; acquisition time = 9 min) were used for identifying moyamoya vessels.