# Basal Ganglia Cerebral Microbleeds and Global Cognitive Function: The Kashima Scan Study

Yusuke Yakushiji, MD, PhD,*† Tomoyuki Noguchi, MD, PhD,‡ Andreas Charidimou, MD, MSc,† Makoto Eriguchi, MD, PhD,* Masashi Nishihara, MD,‡ Megumi Hara, MD, PhD,§ Yusuke Nanri, MD, PhD,* Etsuo Horikawa, PhD,|| Masanori Nishiyama, MD,¶ David J. Werring, MD, PhD,† and Hideo Hara, MD, PhD*

*Background:* We previously showed that global cognitive function was associated with deep or infratentorial (D/I) cerebral microbleeds (CMBs) in a Japanese healthy cohort. We continually recruited participates and performed further investigation to focus on the impact of different distributions of D/I CMBs on gradient-echo magnetic resonance imaging on global cognitive function. *Methods:* A total of 1392 subjects including subjects without CMBs (n = 1335), with D/I CMBs limited to the basal ganglia (BG; BG group, n = 33), thalamus (thalamus group, n = 14), and infratentorial area (infratentorial group, n = 10) were included in analyses. Subjects with strictly lobar CMBs (n = 43) were excluded, but subjects in the BG, thalamus, and infratentorial groups could also have lobar CMBs. The mini-mental state examination (MMSE) was administered to determine global cognitive function; scores less than 27 or more than 1.5 standard deviations (SDs) below the age–education-related mean were regarded as impaired. *Results:* In the multivariable logistic regression analyses, hypertension and severe white matter hyperintensities were associated with the BG group and the thalamus group. In multivariable logistic regression analysis of the association between D/I CMBs classification and impaired MMSE score, only the BG group consistently displayed associations with both MMSE score less than 27 (odds ratio [OR], 5.96; 95% confidence interval [CI], 2.08-17.09) and MMSE score more than 1.5 SDs below the age–education-related mean (OR, 3.34; 95% CI, 1.24-8.99). In the BG group, adjusted mean scores of total MMSE and "attention and calculation" were lower compared with subjects without CMBs. *Conclusions:* In our study of D/I CMBs, only BG CMBs have strong association with global cognitive function. This association was independent of CMBs in other location. **Key Words:** Cerebral microbleeds—small vessel disease—magnetic resonance imaging—cognitive dysfunction—basal ganglia.


From the *Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine, Saga, Japan; †Stroke Research Group, Department of Brain Repair & Rehabilitation, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, United Kingdom; ‡Department of Radiology, Saga University Faculty of Medicine; §Department of Preventive Medicine, Saga University Faculty of Medicine; ||Center for Comprehensive Community Medicine, Saga University Faculty of Medicine, Saga, Japan; and ¶Department of Internal Medicine, Yuai-Kai Oda Hospital, Kashima, Japan.

Received September 1, 2014; accepted September 11, 2014.

The Kashima Scan Study was partially supported by a Grant-in-Aid for University Reform 2006 from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

The authors declare that there are no conflicts of interest.

Address correspondence to Yusuke Yakushiji, MD, PhD, Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine, 5-1-1 Nabeshima, Saga 849-8501, Japan. E-mail: yakushij@cc.saga-u.ac.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.09.015

Vascular cognitive impairment has emerged as an important contributor to cognitive dysfunction in the elderly.[1] Sporadic cerebral small vessel disease (SVD) in particular plays a critical role in cognitive impairment and dementia. Further understanding of the underlying pathophysiologic mechanisms linking SVD and cognitive dysfunction is needed for the prevention of any dementia disorders in the elderly.

Cerebral microbleeds (CMBs), on T2*-weighted gradient-echo magnetic resonance imaging (MRI), are now recognized as an important imaging marker of SVD, in addition to white matter changes and lacunes.[2] CMBs have a different topographic distribution in the brain depending on the underlying SVD: strictly lobar CMBs are characteristic of cerebral amyloid angiopathy (CAA), whereas deep or infratentorial (D/I) CMBs share risk factors and are considered to be mainly associated with hypertensive arteriopathy.[3] CMBs are a promising surrogate marker for SVD-related cognitive dysfunction in stroke patients,[4] memory clinic patients,[5] and neurologically healthy adults.[6]

Increasing attention has been paid to whether different anatomic distributions of CMBs in the brain can have a differential effect on cognitive function,[7-12] but consensus has yet to be reached. We have recently demonstrated that global cognitive dysfunction is associated with D/I CMBs rather than with strictly lobar CMBs in an ongoing Japanese healthy population study.[10] Since then, we have continually recruited participates in this cohort and set out to investigate whether specific D/I CMBs locations might have a different impact on global cognitive function. D/I CMBs are frequently detected in basal ganglia (BG),[4,6,10,13,14] which play an important role in cognitive function.[15] Thus, we hypothesized that, in our population, BG CMBs have the strongest associations with global cognitive dysfunction, independent of other major D/I CMBs, including thalamic CMBs or infratentorial CMBs.

## Subjects and Methods

### *Subjects*

This is a cross-sectional study based on the Kashima Scan Study, an ongoing population-based cohort study investigating age-related brain changes on MRI.[6,10,16] A total of 1739 consecutive adults, who underwent health-screening tests of the brain in our center at their own expense between December 2005 and November 2011, were considered for this study. Inclusion criteria were: (1) 20 years of age or older; (2) no disability in instrumental activities of daily living; (3) ability to independently make visits for current health-screening tests of the brain; and (4) written informed consent. Exclusion criteria were: (1) inability to undergo brain MRI; (2) previous history of any neurologic disorder or brain injury; and (3) abnormalities in the neurologic examination. Of all potentially eligible subjects, 217 individuals refused to enroll, one could not undergo MRI because of claustrophobia, and 13 had a history of neurologic disorder or brain injury with abnormalities seen on MRI. Among the remaining 1508 subjects, 8 subjects displaying motion artifacts on MRI, 1 with numerous cavernous angiomas, and 48 with incomplete data for analysis were excluded. Our final prospective cohort included 1451 subjects (675 men; median age, 58.0 years; range, 22-84 years). All the protocols were approved by our institutional review board. Written informed consent was obtained from all participants in this study.

### *Baseline Assessment*

We recorded clinical characteristics including age, sex, duration of education, smoking status, past history of ischemic heart disease, family history of stroke, presence of hypertension, diabetes mellitus, and dyslipidemia. Hypertension, diabetes mellitus, and dyslipidemia were defined as described elsewhere.[6,10] Past history of ischemic heart disease, family history of stroke and duration of education were obtained from each subject.

All subjects were examined by both a general physician and a certified neurologic surgeon. Global cognitive function was assessed using the mini-mental state examination (MMSE)[17] by a trained nurse. The total score (maximum 30 points) is composed of orientation (10 points), immediate recall (3 points), attention and calculation (5 points), delayed recall (3 points), and language (9 points). We defined impaired MMSE scores by 2 methods. First, according to the MMSE guideline,[18] total scores less than 27 were defined as impaired. Second, according to our recent published normative data of the Japanese MMSE in neurologically healthy cohort (subjects aged ≥40 years, Supplemental Table 1),[19] MMSE scores less than 1.5 SDs below the age- and education-related mean were considered impaired. For subjects 39 years or younger, we used the same cutoff points of 40-44 years category in our previous data.[19] The second method was based on one of the diagnostic criteria used for mild cognitive impairment.[20]

### *Brain MRI*

Brain MRI was performed using a 1.5-T scanner (EXCELART Vantage, version 7.0; Toshiba Medical Systems, Tokyo, Japan) with the following sequences and parameters: axial T1-weighted imaging, repetition time (TR), 550 ms; echo time (TE), 15 ms; flip angle (FA), 80°; section thickness, 7 mm; gap width, 1.4 mm; matrix, 256 × 352 $mm^2$; field of view, 220 × 220 $mm^2$; axial fast spin-echo T2-weighted imaging, TR, 4000 ms; TE, 108 ms; FA, 90°; section thickness, 7 mm; gap width, 1.4 mm; matrix, 352 × 400 $mm^2$; field of view, 220 × 220 $mm^2$, axial fluid-attenuated inversion recovery