Increased Intima Media Thickness and Atherosclerotic Plaques in the Carotid Artery as Risk Factors for Silent Brain Infarcts

Kazuo Inoue, MD, PhD,* Masatoshi Matsumoto, MD, MSc, PhD,† Teiji Shono, MD,* Satoshi Toyokawa, MD, PhD,* and Akihito Moriki, MD, PhD‡

The presence of silent cerebral infarcts (SCIs), defined as lesions ≥ 3 mm in diameter on magnetic resonance imaging (MRI), is considered a predictor of symptomatic cerebrovascular disorders (CVDs). Similarly, SCI-like lesions < 3 mm in diameter, lesions which often occur in the deep white matter and basal ganglia, also may be a risk factor for CVD. This study evaluated the relationships between SCI and SCI-like brain lesions, as defined by MRI, and 2 findings on extracranial carotid ultrasonography: intima-media thickness (IMT) and atherosclerotic plaque. We studied data obtained by carotid ultrasonography and cerebral MRI in 448 consecutive subjects without a history of stroke who had undergone comprehensive brain screening (mean age, 51.1 years). The subjects were classified into 4 groups according to the presence of increased (≥ 1 mm) IMT (I) and plaque (P). A total of 110 subjects demonstrated increased IMT (24.6%), and 54 subjects had increased plaque (12.1%). SCI-like lesions were found in 38 subjects (8.5%); single SCI, in 24 (5.4%); and multiple SCIs, in 51 (11.4%). Frequencies of SCI-like lesion(s), single SCI, and multiple SCIs were 6.1%, 12.2%, and 8.7%, respectively, in the I(−)P(−) group; 14.6%, 22.0%, and 13.4% in the I(+)P(−) group; 7.7%, 30.8%, and 26.9% in the I(−)P(+) group; and 17.9%, 39.3%, and 21.4% in the I(+)P(+) group. Multivariate analysis found that the presence of carotid plaques was significantly associated with (1) SCI-like lesion(s) and SCI (odds ratio [OR] = 2.20; 95% confidence interval [CI] = 1.17–4.34), (2) single and multiple SCI (OR = 2.33; 95% CI = 1.16–4.67), and (3) multiple SCIs (OR = 2.31; 95% CI = 1.06–5.03). However, the presence of increased carotid IMT was not significantly associated with any of these 3 categories. Coexistence of increased IMT and plaque was more strongly correlated with SCI than with either lesion alone. **Key Words:** Carotid plaque—intima media-thickness—silent infarction—magnetic resonance imaging—Japan.

According to criteria for defined by the Japanese Society for the Detection of Asymptomatic Brain Diseases, a silent cerebral infarct (SCI) must be ≥ 3 mm in greatest diameter.[1] An SCI is usually detected by magnetic resonance imaging (MRI) and is considered an important risk factor for stroke. The presence of SCI is often associated with symptomatic stroke,[2-6] cognitive dysfunction,[7,8] and both psychiatric and neurologic disorders.[5,9,10] Enlarged Virchow-Robin (perivascular) spaces, also known as états criblés or a part of deep and subcortical white matter hyperintensity (DSWMH), resemble SCIs in that they appear as bright spots on T2-weighted MRI images, but they usually are < 3 mm in diameter.[1,11-13] Although the pathological significance of these SCI-like lesions has not been elucidated fully, these lesions and SCI appear to be

From the *Department of Public Health, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan; †Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, Tochigi, Japan; and ‡Division of Neurosurgery, Mominoki Hospital, Kochi, Japan.
Received August 11, 2005; revised June 29, 2006; accepted August 11, 2006.
Address reprint requests to Masatoshi Matsumoto, Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498 Japan. E-mail: matmo10@jb3.so-net.ne.jp.
1052-3057/$—see front matter

doi:10.1016/j.jstrokecerebrovasdis.2006.08.001

related, such that SCI-like lesions currently are being investigated as possible indicators of risk for future brain infarction and cognitive dysfunction.[1,14-17]

B-mode ultrasound examination of the carotid artery is noninvasive and has become more widely used than MRI in clinical practice. It is a practical method for examining the walls of peripheral arteries and measuring carotid lesions, including increased intima-media thickness (IMT) and atherosclerotic plaques. Earlier studies have indicated that ultrasound-detected carotid atherosclerotic lesions are associated with ischemic stroke[18,19] and can help estimate the risk of ischemic stroke.[20-25] Accordingly, both the Japanese Society of Hypertension Guidelines for the Management of Hypertension and the European Society of Hypertension/European Society of Cardiology 2003 Guidelines for the Management of Arterial Hypertension have added increased IMT and carotid artery plaques as risk factors for stroke.[26,27]

Although both increased IMT and plaques reflect atherosclerosis in the carotid artery, these lesions have some differences in terms of pathogenesis and clinical significance.[28,29] Thus, a separate evaluation of plaques and IMT may provide better information for determining the risk of atherosclerosis. Several studies have examined the relationship of increased IMT[30-32] and plaques[33-36] with SCI. However, no study has evaluated the situation when both increased IMT and plaque coexist in a single subject, a phenomenon commonly encountered in clinical practice. Little is known about whether the coexistence of the 2 carotid lesions is more strongly associated with SCI than either lesion alone, as well as how the carotid lesions are associated with SCI-like lesions.

Consequently, in the present study we classified the subjects without a history of stroke into 4 groups according to their IMT and/or plaque status and examined the prevalence of SCI and SCI-like lesions in each group. We then assessed the associations of the 2 types of carotid lesions with SCI and SCI-like lesions.

Patients and Methods

Data Collection

We collected data on all 455 asymptomatic adult subjects who participated in the brain screening program at a single hospital between October 1999 and February 2001. If a subject had undergone the screening more than once during the period, then data from the first screening was used for analysis. At the time of screening, body height and weight were measured, and body mass index was calculated. A self-administered questionnaire was used to obtain information on current and past history and treatment, including data on cerebral infarction and hemorrhage, hypertension, coronary heart disease, hyperlipidemia, and arteriosclerosis obliterans. Based on responses to the questionnaire, 7 subjects who reported a history of cerebral infarction were excluded; thus, a total of 448 subjects (316 men and 132 women) were analyzed. The hospital staff coded the collected information so as to blind outside researchers to subject identification. The hospital's ethics committee approved this study.

Carotid Ultrasonography

B-mode ultrasonography of the carotid arteries was performed by trained clinical technicians using a 7.5-MHz linear array transducer and duplex scanner of a Toshiba Power Vision 8000 (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands). Both the right and left common carotid arteries were examined. Carotid IMT was measured in the common carotid arteries (CCAs). IMT was defined as the distance between the media–adventitia interface and the lumina–intima interface[37] and was measured by longitudinal 2-dimensional ultrasound, using image magnification. Any focal thickening of the intima media was excluded from the IMT measurement. IMT measurements were taken at the point of maximal thickness in the walls of both CCAs, using the distance measurement tool in the ultrasound scanner. The measurement was performed to 1 decimal place (in millimeters) and imaged on the scanner display. In a previous study of healthy Japanese subjects ranging in age from 24 to 74 years, the maximum IMT was < 1.0 mm.[38] A cutoff point of 1.0 mm has been used in previous studies and some practice guidelines.[26,27,39,40] We used this same cutoff point and defined a thickened IMT as ≥ 1.0 mm in either or both carotid arteries.

The presence of atherosclerotic plaques, defined as localized lesions with protrusion into the arterial lumen, in CCAs or at bifurcations, was also investigated. As with increased IMT thickness, the presence of plaque was defined as plaque existing in either or both CCAs. Both thickened IMT and plaques were reconfirmed by reexamining the lesions shown on the printouts from the ultrasound scanner. Carotid stenosis was not included in the analysis, because no subjects had severe stenosis ($\geq 50\%$). To examine the impact of the coexistence of increased IMT and plaque on MRI findings, the subjects were categorized into 4 groups according to the absence (−) or presence (+) of increased IMT (I) and plaque (P), thereby forming I(−)P(−), I(+)P(−), I(−)P(+), and I(+)P(+) groups. Then the frequency of each of the abnormal MRI findings observed in each subgroup was assessed and intergroup comparisons were performed.

Brain MRI

Brain MRI was performed, using a GE 1.5-T Signa Echospeed (GE Healthcare, Chalfont St Giles, UK), to obtain T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images (T2-weighted images: TR = 3000 ms, TE = 99.7 ms, BW = 15.6, 8 ch brain coil, FOV = 20 cm,