学 位 論 文 の 要 旨

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学 位 論 文 名　A Prospective Study of Asymptomatic Intracranial Atherosclerotic Stenosis in Neurologically Normal Volunteers in a Japanese Cohort

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論 文 内 容 の 要 旨

INTRODUCTION

Atherosclerotic stenosis of major intracranial arteries is one of leading causes for ischemic stroke in Asia. However, the long-term prognosis of asymptomatic intracranial atherosclerotic stenosis (ICAS) in healthy volunteers has not been fully examined. Furthermore, there has been no longitudinal study investigating the long-term prognosis of ICAS in combination with the role of asymptomatic brain lesions. We performed a prospective study to examine whether ICAS is associated with subsequent stroke onset independent of other risk factors, including asymptomatic brain lesions, in addition to general vascular risk factors in a large number of healthy, elderly Japanese volunteers.

MATERIALS AND METHODS

We originally enrolled a total of 3,161 consecutive Japanese volunteers who voluntarily underwent a medical examination of the brain at the Health Science Center in Shimane between December 2000 and December 2010. The inclusion criteria for this prospective study were as

follows: no history of neurological or psychiatric disorders, including stroke, no abnormalities on neurological examination, and the provision of informed consent to participate in this study. Magnetic resonance imaging (MRI) was performed with a 1.5-T scanner (Symphony Ultra Gradient, Siemens). Vascular stenosis of the main intravascular arteries was assessed: <25% reduction of an arterial diameter was graded as normal; 25 – 49% reduction as mild stenosis; 50 – 74% reduction as moderate stenosis; 75 – 99% reduction as severe stenosis; and no opening as occlusion. Because the volunteers with severe stenosis or occlusion were subjects to medical interventions, we included only subjects with mild or moderate ICAS. The middle cerebral artery (MCA), the intracranial portion of the ICA, the anterior cerebral artery (ACA), the posterior cerebral artery (PCA), and the basilar artery (BA) were evaluated. Silent brain infarction, periventricular hyperintensity (PVH), and the presence of deep and subcortical white matter lesions (DSWMLs) were also assessed. SBI was defined as a focally hyperintense lesion >3 mm in diameter on T2WI, corresponding to a hypointense lesion on T1WI. DSWML and PVH were evaluated separately, because PVH is found adjacent to the ventricles, whereas DSWML is found away from them. PVH was graded using the Fazekas' grading scale.

We excluded volunteers from the analysis who developed intracerebral hemorrhage or subarachnoid hemorrhage during the follow-up period (n = 10). We could not make any contact with 344 volunteers during the follow-up period. As a result, we analyzed data from a total of 2,807 volunteers (1,497 men and 1,310 women; mean age, 62.0 ± 8.5 years), resulting in an 88.8% follow-up rate. Clinical information obtained included age, sex, history of hypertension (defined by the use of an antihypertensive agent, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg), diabetes mellitus (defined as a fasting blood glucose level ≥126 mg/dL, HbA1c ≥6.5%, or a history of treatment for diabetes mellitus), and dyslipidemia (defined as a low-density lipoprotein cholesterol level ≥140 mg/dL, triglyceride level ≥150 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, or a history of treatment with lipid-lowering medication). A smoker was defined as any subject whose smoking index exceeded 200. Regular alcohol consumption was defined as more than 58 mL of alcohol consumed per day. Group differences were analyzed using the Student's t-test or the chi-squared test. Comparisons of cumulative event-free rates for volunteers with or without ICAS were done using Kaplan–Meier curves with the log-rank test. Cox proportional hazards ratios (HRs) were fitted to ICAS data after adjusting for age and other potentially confounding factors. Statistical analysis was performed with the SPSS software package (version 22, IBM Corp., Armonk, NY, USA).

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

Asymptomatic ICAS was observed in 166 volunteers (5.9%), of whom 42 had moderate and 124 had mild ICAS. Moderate and mild stenoses were observed in 1.5 and 4.4% of volunteers, respectively. Significant risk factors for ICAS were older age and a history of hypertension and/or dyslipidemia. During a mean follow-up period of 64.5 months, 32 (1.1%) volunteers had a cerebrovascular event: ischemic stroke in 26 (0.89%) volunteers and TIA in 6 (0.21%) volunteers. Seven strokes occurred in the ICAS group, whose stroke incidence rate was higher than that in the non-ICAS group (0.78 vs. 0.18% per year). We performed a Kaplan–Meier analysis with the log-rank test for volunteers with or without ICAS. There was a significantly higher incidence of ischemic stroke events in volunteers with mild or moderate ICAS compared to that in those without ICAS (P <0.001). In the Cox regression analysis, volunteers with mild or moderate ICAS had significantly higher incidences of ischemic stroke events than those without ICAS after adjusting for age.

Results from the current longitudinal cohort study demonstrated that even mild to moderate asymptomatic ICAS was an independent risk factor for future ischemic stroke in a healthy population. Many studies have confirmed that there is a high risk of vascular events in patients with symptomatic ICAS who had already experienced stroke. Thus, incidental identification of asymptomatic ICAS in healthy volunteers should not be ignored, even when the stenosis is mild.

Elderly people with SBI and DSWML have been reported to be at a highly increased risk of stroke, which could not be explained by other major stroke risk factors. We conducted a logistic regression analysis that incorporated asymptomatic brain lesions into the regression models, and the results showed that asymptomatic ICAS was still a significant predictor for ischemic stroke events. The current study demonstrated that asymptomatic ICAS and DSWML independently contributed to future stroke occurrence. To the best of our knowledge, this is the first study to demonstrate asymptomatic ICAS as an independent risk factor for future stroke, even in healthy volunteers, after adjusting for asymptomatic brain lesions, which are strong risk factors for ischemic stroke. The control of risk factors for ICAS is important for preventing stroke associated with ICAS lesions, because most risk factors are treatable. The current study demonstrated that age, hypertension, and dyslipidemia were independent risk factors for asymptomatic ICAS.

CONCLUSION

Mild to moderate asymptomatic ICAS was a significant risk factor for future stroke, independent of asymptomatic brain lesions, in a healthy Japanese population. Mild to moderate ICAS might be a therapeutic target for stroke prevention.