Associations of Durations of Antiplatelet Use and Vascular Risk Factors with the Presence of Cerebral Microbleeds

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The association of the presence of cerebral microbleeds with antiplatelet use remains controversial. Long durations of antiplatelet use and vascular risk factors may have a greater impact on the development of cerebral microbleeds than short durations. The aim of this study was to determine whether the durations of antiplatelet use and vascular risk factors were associated with the presence of cerebral microbleeds in patients with ischemic cerebrovascular disease, who are frequently treated with antiplatelet agents. Two hundred twenty outpatients with ischemic cerebrovascular lesions (eg, cerebral infarcts and/or white matter lesions) detected by magnetic resonance imaging were examined. Patients with a history of cerebral hemorrhage were excluded. Cerebral microbleeds were observed in 71 (32.3%) patients. Deep or infratentorial microbleeds and strictly lobar microbleeds were observed in 53 (24.1%) patients and 18 (8.2%) patients, respectively. Aspirin use (odds ratio, 2.14; 95% confidence interval [CI], 1.02-4.73; $P = .04$) and a long duration (≥10 years) of aspirin use (odds ratio, 3.75; 95% CI, 1.31-10.86; $P = .01$) were significantly associated with deep or infratentorial microbleeds in the crude analysis, but this became nonsignificant after adjustment for hypertension and other confounding factors. The prevalence of antiplatelet use was significantly higher in the patients with hypertension than in those without hypertension (72.5% versus 49.1%, $P = .002$). Hypertension (odds ratio, 2.50; 95% CI, 1.11-6.41; $P = .04$) was significantly associated with the development of deep or infratentorial microbleeds even after adjustment for confounding factors and the association increased with the duration of hypertension. In conclusion, we found a significant association between aspirin use and deep or infratentorial microbleeds, but this association may reflect the presence of hypertension as a confounding factor. **Key Words:** Antiplatelet agents—cerebral microbleeds—hypertension—ischemic cerebrovascular disease.

Introduction

Cerebral microbleeds are neuroimaging findings that can be detected by gradient-echo T2*-weighted magnetic resonance imaging (MRI). Histopathologic examination showed that they are focal hemosiderin depositions in perivascular space.[1] Cerebral microbleeds in a deep or infratentorial region are related to hypertensive vasculopathy, whereas those in strictly lobar region are related to cerebral amyloid angiopathy.[2] The presence of cerebral microbleeds indicates hemorrhage-prone pathological states and predicts the risk of future symptomatic intracerebral hemorrhage.[3,4] Furthermore, cerebral microbleeds are associated with cognitive dysfunction in stroke patients[5] and adults without neurological disorder.[6]

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Because patients with ischemic cerebrovascular disease are frequently treated with antiplatelet agents, the investigation of the effects of antiplatelet use on the development of cerebral microbleeds in these patients is very important. However, the association between antiplatelet use and the presence of cerebral microbleeds remains controversial. Previous studies have shown that antiplatelet use is significantly associated with the presence of cerebral microbleeds among patients with ischemic stroke,[3] cerebral hemorrhage,[7] and those with Binswanger's disease and multiple lacunar infarction.[8] The presence of cerebral microbleeds in a strictly lobar region but not in a deep or infratentorial region is associated with antiplatelet use in the general population aged 60 years and older.[9] Pooled analysis demonstrated that antiplatelet use is related to excessive cerebral microbleeds in intracerebral hemorrhage but not in ischemic stroke/transient ischemic attack.[10] However, other studies showed no association of antiplatelet use with the presence of cerebral microbleeds in patients with ischemic stroke,[7,11,12] intracerebral hemorrhage,[13-15] and in cohorts of patients with mixed ischemic and hemorrhagic stroke.[16,17] Long durations of antiplatelet use and vascular risk factors may have a greater impact on the development of microbleeds than short durations. However, the durations of antiplatelet use and vascular risk factors were not evaluated in those previous studies. The aim of this study was to determine whether the durations of antiplatelet use and vascular risk factors were associated with the presence of cerebral microbleeds in patients with ischemic cerebrovascular disease.

Methods

Patients

We examined outpatients who visited the Department of Neurology, Juntendo University Shizuoka Hospital from December 2010 to February 2012. Patients with a history of vascular risk factors (ie, hypertension, diabetes mellitus, dyslipidemia, and smoking) and those newly diagnosed as having these risk factors were examined by brain magnetic resonance imaging (MRI). Patients who had a history of cerebral hemorrhage and MRI contraindications such as having an implanted pacemaker were excluded. Two hundred twenty patients whose brain MRI showed ischemic cerebrovascular lesions (ie, cerebral infarcts and/or white matter lesions) were included in this study. All the study participants provided informed consent, and the study design was approved by the Institutional Review Board of the hospital. The durations of antiplatelet use and vascular risk factors were examined from medical records and/or by interview. The durations of vascular risk factors were categorized into 3 groups (>0 and <10, ≥10 and <20, and ≥20 years). Patients newly diagnosed as having vascular risk factors were included in the group of >0 and <10 years. Hypertension was defined as having a systolic blood pressure of 140 mm Hg or more and/or a diastolic blood pressure of 90 mm Hg or more and/or taking antihypertensive treatment. Diabetes mellitus was defined as having a nonfasting blood glucose level of 200 mg/dL or more and/or an HbA1c level of 6.5% or more and/or using insulin or oral hypoglycemics. Dyslipidemia was defined as having a total cholesterol level of 220 mg/dL or more and/or a triglyceride level of 150 mg/dL or more and/or using lipid-lowering medication. The durations of antiplatelet use were categorized into 2 groups (>0 and <10 and ≥10 years). We also examined the durations of the use of aspirin and thienopyridine (ticlopidine or clopidogrel) among antiplatelet agents.

Brain MRI

MRI was performed using a 1.5-T MR system (Magnetom Avanto; Siemens, Erlangen, Germany), and the whole brain was scanned at a slice thickness of 6 mm and an interslice gap of 1.2 mm, obtaining 19 axial images. The imaging protocol consisted of T2*-weighted gradient echo (repetition time [TR]/echo time [TE] = 685/25 ms; flip angle, 20°), T1-weighted spin echo (TR/TE = 500/13 ms), T2-weighted fast spin echo (TR/TE = 3800/91 ms), and fluid-attenuated inversion recovery (TR/TE = 8500/79 ms, inversion time 2500 ms). Cerebral microbleeds were defined as small, homogeneous, round foci of low signal intensities on T2*-weighted images and of less than 10 mm diameter. Hypointense lesions within the subarachnoid space or those possibly associated with calcification were excluded. Microbleeds were categorized into 3 types according to the region of their localization: deep (basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter), infratentorial (brainstem or cerebellum), and lobar (cortical or subcortical regions) microbleeds. A lacunar infarct was defined as a small, deep infarct of less than 15 mm diameter, with a low signal intensity on T1-weighted images. White matter lesions were evaluated by using a semiquantitative method proposed by Fazekas et al.[18] Periventricular hyperintensity (PVH) was graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo," and 3 = irregular PVH extending into the deep white matter. Deep white matter hyperintensity (DWMH) was graded as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas.

Data Analysis

A previous study has shown that deep or infratentorial microbleeds and strictly lobar microbleeds are associated with hypertensive microangiopathy and amyloid angiopathy, respectively.[2] Thus, we categorized the patients on the basis of the location of microbleeds described previously.[2] The patients were divided into 2 groups according