Background and Purpose—Cerebral microbleeds (CMBs) are known to be indicative of bleeding prone microangiopathy. Little is known about its significance in anticoagulated patients. We aimed to determine the frequency of CMBs in ischemic stroke patients on warfarin treatment.

Methods—A total of 141 ischemic stroke patients on warfarin therapy were enrolled in this study. One hundred five patients with similar demographic features who do not use warfarin were chosen as controls. We compared vascular risk factors and radiological findings including CMBs and leukoaraiosis between the groups.

Results—CMBs on gradient-echo MRI (GE-MRI) were found in 31 patients (22%) and 17 controls (16%) and there was not a significant difference between 2 groups ($P=0.25$). Study patients with CMBs were older than patients without CMBs ($P=0.04$) and frequency of leukoaraiosis was significantly higher ($P=0.008$). Mean duration of warfarin treatment was not different between the patients with and without CMBs ($P=0.83$).

Conclusion—Although patients with CMBs were older and had more leukoaraiosis the impact of warfarin treatment on CMBs is still controversial. (Stroke. 2009;40:3638-3640.)

Key Words: cerebral microbleeds ▪ warfarin ▪ ischemic stroke ▪ magnetic resonance imaging

Although warfarin is used effectively for the prevention of atrial fibrillation related cardio-embolic infarction, randomized controlled trials demonstrate a 2- to 4-fold increase in the rate of intracerebral hemorrhage (ICH) among patients treated with it. The mortality rate was also reported to increase in these patients with hemorrhage. Therefore, identification of risk factors for bleeding and preventing ICH in patients on warfarin therapy is extremely important.

Cerebral microbleeds (CMBs) are seen as small round hypointense lesion on T2-weighted gradient-echo MRI (GE-MRI) and correspond histopathologically to deposits of hemosiderin from previous bleeding. CMBs can be detected in more than half of the patients with primary ICH, predict future occurrence or reoccurrence of ICH, and may be indicative of a bleeding prone state in the brain.

The aim of this case–control study was to determine the frequency of CMBs in ischemic stroke patients on warfarin treatment.

Materials and Methods

Among 160 patients who had ischemic cerebrovascular disease, treated with warfarin and being followed-up in the Cerebrovascular Diseases outpatient clinic, 141 who did not have any contraindication for cranial MRI examination were included to this prospective study. They had MRI examination on their routine outpatient visit. One hundred five subjects were chosen as controls consecutively among hospitalized patients for acute ischemic stroke who were candidates for warfarin treatment and those who used warfarin previously were excluded. After recruitment all control subjects had MRI examinations before the warfarin treatment began.

The study was approved by institutional review committee, and informed consent was obtained from the patients or the caregivers.

MRI examination of brain was performed on 1.5-T superconducting magnet with a standard head coil (Signa Excite 2.0, GE Healthcare). The protocol included initial acquisition of a scout image (repetition time ms/echo time ms, 15/6), followed by application of the following sequences: T1-weighted spin echo (575/14; section thickness, 6 mm; field of view, 210 mm; matrix, 256×256), T2-weighted fast spin echo (2,474/17, 102; section thickness, 6 mm; field of view, 210 mm; matrix, 256×256), axial T2-weighted gradient-echo sequences (TR/TE 640/15 ms, flip angle 15°), fluid-attenuated inversion recovery (FLAIR; repetition time ms/echo time ms/inversion time ms, 9000/110/1800; section thickness, 5 mm; field of view, 240 mm; matrix, 256×256). Focal areas of homogeneous round signal loss in brain parenchyma measuring <5 mm areas on GE-MRI sequences were identified as CMBs. The numbers of CMBs was counted on whole brain area by 2 authors (D.N.O. and E.U.) separately and determined by consensus. Lesions within the sulcal areas and areas of symmetrical hypodensity of globus pallidus, likely to represent adjacent pial blood vessels and calcification respectively, were not included. We classified the degree of CMB as absent, mild (1–5), moderate (5–10), and severe (>10) according to Lee et al. Leukoaraiosis was classified as punctuate, early confluent, and confluent by using the method described by Fazekas et al.

Hypertension was considered present when a patient had received antihypertensive treatment before admission or when hypertension was diagnosed during the hospital stay by repeated detection of blood pressure ≥160/90 mm Hg. A diagnosis of diabetes mellitus (DM) was based on a history of DM with or without current treatment or two fasting plasma glucose levels of 126 mg/dL or higher. A diagnosis of hypercholesterolemia was based on history of
hypercholesterolemia with medication or a fasting serum cholesterol level $>220$ mg/dL. A history of smoking was coded if a subject was a current smoker or an ex-smoker who had quit smoking 5 years of admission. Alcohol was accepted as a risk factor if current consumption reached to 300 g/wk. Indications for warfarin included major cardioembolic sources, minor cardioembolic sources, and other causes.

Descriptive and frequency statistical analysis were obtained and comparisons were made using the SPSS 11.5 statistical package. Evaluation of the data were by definition of mean $\pm$SD. Comparisons for clinical variables between patients who had CMBs or not were performed by using unpaired $t$ test and $\chi^2$ test as appropriate. The threshold level for statistical significance was established at $P<0.05$.

### Results

Demographic features of patients and controls are shown in Table 1. None of the risk factors were significantly different between 2 groups. Seventy-five patients and 61 controls had leukoaraiosis, and there was no significant difference between groups ($P=0.31$). CMBs on GE-MRI were found in 31/1100 patients (22%) and 17 controls (16%), and there was not a significant difference between 2 groups. Seventy-five patients and 61 controls had CMBs. The frequency of leukoaraiosis was significantly higher in patients with CMBs ($P=0.008$). Mean duration of warfarin treatment was 3.80 $\pm$ 3.77 and 3.94 $\pm$ 3.05 years respectively in patients with and without CMBs ($P=0.83$). Distribution of patients according to treatment duration was shown in the Figure. Nine patients (29%) with CMBs and 34 (31%) without CMBs were on warfarin treatment more than 5 years ($P=0.84$). During study period, intracranial bleeding was seen in 2 of 23 patients with bleeding complications, which of one was CMB (+).

### Discussion

In this case–control study, although the frequency of CMBs in stroke patients on warfarin treatment was higher than the controls, it did not reach statistical significance. Patients who had CMBs were older and had more leukoaraiosis, and we did not find any association with the duration of therapy.

Fazekas et al performed a histopathologic analysis of cerebral microbleeds visualized on GE-MRI and confirmed that these regions indicate previous extravasation of blood and are related to bleeding prone microangiopathy. It was suggested that these lesions might be indicative of a bleeding prone state in ICH and hemorrhagic transformation after acute ischemic stroke. Nighoghossian et al demonstrated increased hemorrhagic transformation in patients with CMBs and suggested that the associated vascular vulnerability contributes to hemorrhagic transformation. According to Cochrane Database, treatment with adjusted-dose warfarin to achieved INRs of 2 to 3 reduces disabling or fatal stroke and death for patients with nonvalvular atrial fibrillation. The benefits were not reported to be substantially offset by...
increased bleeding among these participants in randomized clinical trials.\(^\text{10}\) Leukoaraiosis and lacunar state of the basal ganglia are frequently observed in patients who experienced ICH under warfarin therapy. Both abnormalities have been suggested to indicate a higher risk of bleeding.\(^\text{11}\) Leukoaraiosis is an independent risk factor for warfarin-related ICH in survivors of ischemic stroke, including those in the commonly used range of anticoagulation.\(^\text{12}\) Several other risk factors for warfarin-related ICH have been reported. Advancing age, cerebral amyloid angiopathy, prior cerebrovascular diseases, and higher intensities of anticoagulation are important contributory factors to oral anticoagulant related ICH.\(^\text{13}\)

Recently, Lee at al found that prothrombin time and the presence of microbleeds on GE-MRI were independently associated with the incident ICH in the patients undergoing warfarin treatment.\(^\text{14}\)

A pooled analysis of 210 subjects with ischemic stroke, ICH, and heterogeneous disorders demonstrated that anticoagulant agents are not associated with an increased risk of CMBs.\(^\text{15}\) Our study is the first prospective one that evaluates the effect of warfarin treatment on CMBs in a homogenous ischemic stroke population using warfarin approximately 4 years.

There are some limitations in this study. First, the time interval of patients’ follow-up was inadequate to evaluate the ICH risk in patients with CMBs. Second, as the indications of warfarin treatment consisted of largely the young patients with cardioembolic stroke, the low rate of CMBs and leukoaraiosis in our population may not be representative for older stroke patients. Third, the drop-out of such patients with severe bleeding complications in outpatient clinic also may be the reason of the negative findings in this study. Fourth, as this was a cross-sectional designed study, we were unable to comment that CMBs were solely related to warfarin treatment or not.

In conclusion, the impact of warfarin treatment on CMBs is still controversial. Because the GE-MRIs of our control group was performed at baseline before warfarin treatment, we propose that future evaluations of these patients will provide us more information about risk of CMBs in patients on warfarin therapy.

Disclosures

None.

References

Cerebral Microbleeds in Ischemic Stroke Patients on Warfarin Treatment
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