Microbleeds and the Risk of Recurrent Stroke

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Background and Purpose—We studied the risk of recurrent cerebrovascular events in patients who had a transient ischemic attack or ischemic stroke and who had evidence of microbleeds on MRI.

Methods—A prospective follow-up study was performed on hospitalized patients who were at least 50 years old with a transient ischemic attack or an ischemic stroke. The presence and number of microbleeds were assessed on gradient echo MRI and the presence of white matter disease on fluid-attenuated inversion recovery imaging using a semiquantitative scale. Patients were followed up by phone every 6 months. End points were intracerebral hemorrhage, ischemic stroke, and unclassified stroke. Cerebral events were adjudicated by 2 independent neurologists blinded to the presence of microbleeds. Cox regression analysis was performed.

Results—A total of 487 patients with a mean age of 72 years were followed up for a median of 2.2 years (25th to 75th percentile 1.9 to 2.7 years). Microbleeds were identified in 129 patients (25.6%). Two patients developed intracerebral hemorrhage during follow-up, 32 patients developed recurrent ischemic stroke, and 3 patients had unclassified strokes. Microbleeds were not independent predictors of recurrent stroke (P=0.2) or intracerebral hemorrhage (P=0.43). Lobar microbleeds or combined lobar and deep microbleeds were independently associated with recurrent stroke (P=0.018).

Conclusion—In this European cohort, patients with microbleeds who have had cerebral ischemia have a higher risk of developing new ischemic strokes than of intracerebral hemorrhage. Lobar microbleeds or combined lobar and deep microbleeds might be independent predictors of recurrent stroke. (Stroke. 2010;41:2005-2009.)

Key Words: antiplatelet Rx ■ antithrombotics ■ intracranial hemorrhage ■ lacunar infarcts ■ lacunes ■ leukoaraiosis ■ magnetic resonance ■ neuroradiology ■ stroke care ■ white matter disease

Microbleeds are commonly observed on gradient echo MRI (GRE) of normal elderly individuals and in patients with ischemic and hemorrhagic stroke.1–3 They probably represent hemosiderin-laden macrophages resulting from microhemorrhages.4 Microbleeds are strongly associated with the presence of white matter hyperintensities on MRI.5

The presence of microbleeds might predict the occurrence of cerebral hemorrhagic complications in patients undergoing stroke thrombolysis or predict development of intracerebral hemorrhage in patients treated with oral anticoagulants or antiplatelet agents.6–8 Studies showing an increased risk of intracerebral hemorrhage in patients with microbleeds after lacunar stroke or ischemic stroke in general were mainly performed in Asian populations.9–12 One study from outside Asia suggested that patients with microbleeds have a higher risk of incident ischemic stroke.13

We assessed whether microbleeds were associated with incident intracranial hemorrhage or recurrent ischemic stroke in European patients with transient ischemic attack or stroke.

Methods

European patients aged ≥50 years who were admitted to the Stroke Unit of the University Hospitals in Leuven, Belgium, between July 2003 and May 2005 and who survived at least 7 days after stroke were included. Patients who were unable to undergo MRI examination were excluded. Informed consent was obtained. Surrogate consent was permitted. The only information recorded on patients who did not participate in the study was age and sex. The study was approved by the Ethics Committee of the University Hospitals in Leuven. We recorded age at admission, sex, hypertension (defined as use of antihypertensive medication or physician-measured blood pressure >140/90 mm Hg before stroke onset), diabetes mellitus (fasting glucose >125 mg/dL or use of antidiabetic medication), fasting cholesterol levels, and current smoking of the patients. Glucose levels were obtained after stroke. In patients with elevated fasting glucose levels, glycosylated hemoglobin measurements were obtained and an endocrinologist was consulted to make a final diagnosis of diabetes mellitus. A history of stroke was noted. Coronary artery disease was defined as history of myocardial infarction, coronary artery bypass grafting, coronary angioplasty, or stenting or angina pectoris. Hyperlipidemia was defined as elevated fasting total cholesterol levels or pre-stroke statin use. We also recorded which antithrombotic strategy was started at discharge. Patients were classified into stroke subgroups based on the Trial of...
Magnetic Resonance Imaging
All patients underwent an acute stroke imaging protocol, including sagittal T1-weighted, axial T2-weighted, fluid-attenuated inversion recovery imaging plus diffusion-weighted imaging and GRE. MRI scans were performed on a Siemens Magnetom Expert with a field strength of 1.5 T or a Siemens Symphony Vision 1.5-T system or a Philips Intera 1.5- or 3-T system. The GRE sequences were as follows: TR 1000 ms; TE 35 ms (Siemens Magnetom Expert) and TR 710 ms; TE 26 ms (Siemens Vision) and TR 917 ms; and TE 16 ms (Philips Intera). The GRE imaging was obtained in the axial plane with the following parameters: 7-mm slice thickness, field of view 240 mm, 60° flip angle, and 256×256 matrix.

Cerebral Microbleeds
Microbleeds were defined as homogeneous round hypointense lesions of diameter ≤5 mm on GRE MRI. Hypointense lesions within the subarachnoid space and areas of symmetrical hypointensity in the globus pallidus on GRE were considered to represent adjacent pial blood vessels or calcifications and were excluded. The number and location of microbleeds were assessed independently by trained observers (3 neurologists, 1 radiologist, and 1 neuroradiologist). Each GRE was rated by 2 observers. In case of disagreement between the 2 initial observers, the neuroradiologist made the final determination. The observers had access to the diffusion-weighted imaging to avoid regions of hemorrhagic transformation in the assessment of microbleeds. The locations of the microbleeds were classified by cerebral region as follows: lobar or nonlobar (basal ganglia, thalamus, and infratentorial area [brain stem, cerebellum]).

White Matter Disease
Fluid-attenuated inversion recovery imaging images were analyzed using a modified semiquantitative rating scale devised by Fazekas et al. This method yields 2 separate brain white matter disease scores: (1) subcortical and deep white matter lesions; and (2) periventricular lesions. Each variable was scored on a scale of increasing severity. White matter lesions were scored by the following: 0, normal; 1, punctate; 2, coalescing; and 3, confluent. Periventricular lesions were scored by the following: 0, normal, pencil lines and/or caps, smooth haloes; and 1, irregular. For statistical analyses, white matter disease severity, defined as the sum of the scores on the white matter lesion and periventricular lesion rating scale, was dichotomized into scores 0 or 1 (absent or mild) versus 2 or more (moderate to severe).

Follow-Up of Patients
The inception date of follow-up was the time of initial stroke diagnosis. All patients were seen at a follow-up examination 3 to 6 months after hospital admission. Subsequently, a trained study nurse contacted the patients or the primary care physician every 6 months to assess the presence of recurrent acute cerebral events or death. If the patients or the primary care physician reported new events, we obtained the hospital charts and requested brain imaging reports. Loss to follow-up was defined as patients not returning to their follow-up examination or who could not be traced back after the clinic visit.

End Point Adjudication
Two neurologists (P.V.D., M.S.) independently reviewed the charts and the radiology reports of patients with recurrent cerebral events. Information on the presence of microbleeds was carefully removed before adjudication to avoid unblinding of the observers.

End Points
End points were intracerebral hemorrhage, recurrent ischemic stroke, and unclassified stroke. A recurrent ischemic stroke was defined as the sudden onset of a new focal neurological deficit lasting either >24 hours or leading to death with absence of hemorrhage on acute CT or with a new ischemic lesion on diffusion-weighted imaging. Intracerebral hemorrhage was defined as the sudden onset of a new neurological deficit with hemorrhage within the brain parenchyma. Unclassified stroke was defined as the sudden onset of a new focal neurological deficit lasting >24 hours or leading to death in which cerebral imaging or autopsy was not obtained. Deaths were divided into vascular death or nonvascular death. Deaths were considered of vascular origin unless a clear alternative diagnosis like cancer or trauma was identified.

Statistical Analysis
Baseline characteristics were compared using the χ² test or the Student t tests as appropriate. Log-rank analysis was performed to compare whether microbleeds were associated with a higher end point rate. Cox regression analysis was performed with microbleeds as an independent factor and as covariates the baseline factors that were significantly different between the 2 groups after checking the proportionality assumption. Cumulative incidence estimates were calculated. These provide more reliable risk estimates when there is a relatively high frequency of other competing events like nonvascular death that prevent the end point of interest from occurring. All tests were 2-tailed and a probability value of <0.05 was considered significant. All statistical tests were performed using Statistical Package for the Social Sciences 16.0 or R: A Language and Environment for Statistical Computing. Reference Index Version 2.1.0 (R Foundation for Statistical Computing).

Results
Between July 2003 and May 2005, 783 patients aged ≥50 years with suspected transient ischemic attack or ischemic stroke were admitted to the Stroke unit. Four hundred eighty-seven patients (62%) participated in the study. Patients who did not participate had a similar age (73 versus 72 years, P = 0.33), but were more frequently female (49% versus 39%, P = 0.02). The main reasons for nonparticipation were a nonstroke final diagnosis or, during the first part of the study, the nonsystematic performance of GRE sequences by the MR technician. A previous paper reported on the association of apolipoprotein E with white matter disease and microbleeds in a subgroup of the included patients. The baseline characteristics of the included patients are shown in Table 1. Of the 352 patients with ischemic stroke, we included 190 patients (54%) with a partial anterior circulation syndrome, 30 patients (9%) with a total anterior circulation syndrome, 67 patients (19%) with a posterior circulation syndrome, and 65 patients (18%) with a lacunar syndrome.

MRI was performed at 1 T in 139 patients (29%), at 1.5 T in 244 patients (50%), and at 3 T in 104 patients (21%). Microbleeds were identified in 129 patients (25.6%). Multiple microbleeds were present in 75 of 129 patients (58%). There was no higher frequency of detection of microbleeds with higher magnetic field strengths (P = 0.16). Microbleeds were located in the lobar region in 59 patients (46%), in mixed locations in 45 patients (35%), and in nonlobar regions in 25 patients (19%). The interobserver reliability for the presence of microbleeds was substantial (κ = 0.71, 95% CI 0.63 to 0.78).

At baseline, patients with microbleeds more frequently had severe white matter disease and a stroke history (Table 1). There were slight borderline significant differences in Triol of Org 10172 in Acute Stroke Treatment categories with more small vessel disease and less frequent cryptogenic or other determined causes in patients with microbleeds. The anti-
Follow-Up and End Points

The median follow-up duration was 2.2 years (25th percentile to 75th percentile 1.9 to 2.7). Eight patients (1.6%) were lost to follow-up. At 1 year, there were 432 (89%) patients alive without events and still in follow-up. At 2 years, there were 313 (64%) patients alive without events and still in follow-up. There were 32 ischemic strokes (6.6%), 2 intracerebral hemorrhages (0.4%), 3 unclassified strokes (0.6%), 19 non-stroke vascular deaths (3.9%), and 25 nonvascular deaths 5.1% during the 805 person-years of follow-up.

Microbleeds and Recurrent Events

Microbleeds were not associated with a higher rate of intracerebral hemorrhage; 1 intracerebral hemorrhage occurred in a patient with multiple lobar microbleeds and 1 intracerebral hemorrhage occurred in a patient without microbleeds at baseline (log-rank test, \( P=0.43 \)). Assuming the worst case scenario that all recurrent unclassified strokes in the patients with microbleeds were intracerebral hemorrhage and that all of the unclassified strokes in patients without microbleeds were ischemic, there still was no association between the presence of microbleeds and intracerebral hemorrhage (log-rank test, \( P=0.09 \)).

There was an almost significant association between microbleeds and recurrent ischemic stroke with 13 events occurring in 129 patients with microbleeds and 19 events in 358 patients without microbleeds (log-rank test, \( P=0.054 \)). There was an association with total stroke in univariate analysis with 15 events in patients with microbleeds and 22 events in patients without microbleeds (log-rank test, \( P=0.038 \)).

Microbleeds and Recurrent Stroke

Table 2 shows the annual risks of any recurrent stroke in various groups of patients. In multivariate analysis, correcting for stroke history and white matter disease, microbleeds were not associated with a higher total stroke rate. There were no recurrent strokes in patients with nonlobar microbleeds (\( n=25 \)). Only patients with lobar or mixed microbleeds had recurrent strokes in the patients with microbleeds. This association remained significant after correction for stroke history (hazard ratio 2.4 [95% CI 1.2 to 5.0]) and white matter disease (hazard ratio 1.7 [95% CI 0.9 to 3.3]). Additional correction for the slight imbalances in stroke subtypes or the MRI field strength did not alter the findings (data not shown). The association remained also present after correction for age, sex, and diabetes with a hazard ratio of 2.1 (95% CI 1.1 to 4.2, \( P=0.03 \)). Both pure lobar microbleeds (hazard ratio 2.3, 95% CI 1.02 to 5.19, \( P=0.04 \)) and microbleeds in mixed locations (hazard ratio 2.7, 95% CI 1.2 to 6.4, \( P=0.02 \)) were associated with recurrent stroke.

The presence of multiple microbleeds was not independently associated with a higher total stroke rate. Also, when the analysis was restricted to patients treated with antithrombotic agents with a higher risk of hemorrhagic complications, no association was found.

Discussion

Our analysis suggests that microbleeds signal an elevated risk of recurrent stroke. The large majority of recurrent events...
with microbleeds were ischemic rather than hemorrhagic. An independent effect of microbleeds on the development of recurrent stroke was not present. For clinicians, this implies that, at present, strategies to prevent recurrent stroke should not be altered when microbleeds are found on neuroimaging.

It has been proposed that lobar and nonlobar microbleeds have a different pathophysiological background with lobar microbleeds resulting from amyloid deposition and nonlobar microbleeds from leakage of blood products through vessels damaged by hypertension. We found that patients with exclusively lobar or a mix of lobar and deep microbleeds had an independent risk of recurrent stroke in a post hoc analysis. The interpretation of this finding is not straightforward. Amyloid deposition is typically associated with the development of intracerebral hemorrhage, although ischemic events have also been described. The presence of microbleeds in both lobar and deep locations might be a marker of severe cerebrovascular burden or signal the presence of a combination of hypertensive damage and amyloid angiopathy. The finding of an elevated risk of recurrence in lobar or mixed microbleeds may also have arisen by chance because of multiple hypothesis testing. Further studies are needed to replicate this finding, although they accord with 1 prospective study in which a similar finding was observed.

Six prospective controlled cohort studies have examined the association between microbleeds and subsequent stroke risk in patients with a history of transient ischemic attack or ischemic stroke. Three studies were performed in Asia. A higher rate of recurrent stroke, in the majority hemorrhagic, was noted in a prospective study when multiple lobar microbleeds were present, but this study combined patients with lacunar stroke and intracerebral hemorrhage and did not present results separately for lacunar stroke or intracerebral hemorrhage. One small study found a borderline significantly increased risk of intracerebral hemorrhage after ischemic stroke. A follow-up study, including the same patients as the former study, in a larger population with a longer duration of follow-up showed a significantly increased risk of intracerebral hemorrhage, especially with multiple microbleeds. In a Japanese study, a higher rate of intracerebral hemorrhage was found in patients with microbleeds and advanced white matter disease and a higher risk of ischemic stroke in patients with advanced white matter disease without microbleeds. Our findings concur with the only relatively large study performed in a Canadian population, which also found an elevated risk of recurrent cerebrovascular events, mainly ischemic, in patients with microbleeds. Similar to our study, only 2 recurrent intracerebral hemorrhages were observed during a median follow-up of 14 months in 236 patients. One recent, small prospective study in the United Kingdom found 1 recurrent intracerebral hemorrhage in 8 patients followed up for 5 years with microbleeds compared with no intracerebral hemorrhage in 13 patients without microbleeds.

Our study has several limitations. Our sample size was relatively small as was the number of end point events, especially intracerebral hemorrhages. The small number of end points did not permit correction for all potential predictors of recurrent stroke. We therefore cannot exclude residual confounding. We think that a definite answer on the role of microbleeds will only be derived from large, multicenter studies or as a substudy from large, randomized clinical trials that obtained standardized MRIs. Microbleeds were measured on different MRI scanners with different field strengths. The choice of MR scan was based on the availability of the MR scan and not based on clinical parameters, limiting selection bias. We also used conventional GRE images rather than thin-section susceptibility weighted images. These have been shown to improve the detection of microbleeds. This may have led to partial misclassification in some patients and our results can therefore not be directly extrapolated to those obtained with susceptibility weighted images. We did not use a published scale for microbleed rating but an in-house published scale. The treating physicians were not blinded to the presence of microbleeds and this may have influenced the antithrombotic regimen at discharge. However, we have no evidence that this led to changes in antithrombotic management because the discharge medication used was similar in patients with or without microbleeds. The follow-up of a limited number of patients was by contact with the primary care physician who may not have been aware of all new strokes.

In conclusion, in this European cohort, microbleeds are indicative of a higher recurrent stroke risk but do not seem to signal a very high risk of intracerebral hemorrhage because most recurrences are ischemic in nature. Lobar microbleeds or the simultaneous presence of microbleeds in lobar micro-

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**Table 2. Estimated Cumulative Recurrent Total Stroke Rates**

<table>
<thead>
<tr>
<th></th>
<th>Estimated Risk at Year 1 (95% CI)</th>
<th>Estimated Risk at Year 2 (95% CI)</th>
<th>Unadjusted P (Log-Rank Test)</th>
<th>Adjusted† HR (Cox Regression)</th>
<th>Adjusted† P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any microbleed</td>
<td>7.8 (4.0–13.3)</td>
<td>10.3 (5.8–16.4)</td>
<td>0.04</td>
<td>1.6 (0.8–3.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Single microbleed</td>
<td>3.7 (0.7–11.4)</td>
<td>7.8 (2.4–17.2)</td>
<td>0.40</td>
<td>1.3 (0.5–3.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Multiple microbleeds</td>
<td>10.8 (5.0–19.1)</td>
<td>12.1 (5.9–20.8)</td>
<td>0.02</td>
<td>1.9 (0.8–3.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lobar or mixed microbleeds‡</td>
<td>9.7 (4.9–16.4)</td>
<td>12.8 (7.2–20.4)</td>
<td>0.005</td>
<td>2.4 (1.2–5)</td>
<td>0.018</td>
</tr>
<tr>
<td>High risk antithrombotic strategy with ± 1 microbleed</td>
<td>9.0 (2.8–19.7)</td>
<td>13.8 (5.5–25.8)</td>
<td>0.13</td>
<td>1.7 (0.7–4)</td>
<td>0.26</td>
</tr>
<tr>
<td>No microbleeds</td>
<td>5.1 (3.1–7.7)</td>
<td>5.9 (3.8–8.7)</td>
<td>Reference</td>
<td>Reference</td>
<td>…</td>
</tr>
</tbody>
</table>

*Risk estimates are corrected for competing nonstroke mortality.
†Corrected for baseline imbalances in white matter disease and prestroke history.
‡No events occurred in the patients with exclusively nonlobar microbleeds: Risk estimates cannot be calculated.
leeds and deep regions may indicate a particularly high recurrent stroke risk.

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