Cerebral Microbleeds Are Associated With Lacunar Stroke Defined Clinically and Radiologically, Independently of White Matter Lesions

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Background and Purpose—Associations among microbleeds, white matter lesions (WMLs), and small deep infarcts on imaging have been reported. Because many of these imaging infarcts were asymptomatic, the relationship of microbleeds to clinical lacunar stroke is unclear. An association between microbleeds and clinically defined lacunar stroke might suggest a common causal microangiopathy.

Methods—Patients with lacunar, partial anterior circulation or posterior circulation stroke syndromes and older healthy subjects underwent MRI. Microhemorrhages, infarcts, hemorrhages, and WMLs were coded blind to clinical details. A final clinicoradiologic stroke subtype diagnosis was assigned.

Results—Among 308 subjects (67 older healthy and 241 with stroke), 54 patients had microbleeds (17%). Microbleeds were twice as frequent in lacunar than cortical strokes (26% versus 13%, \( P = 0.03 \)) or healthy older subjects (9%) and associated with increasing WML scores (\( P < 0.0001 \)). Lacunar and cortical stroke subtypes and healthy older subjects had similar WML scores.

Conclusions—Microbleeds are associated with lacunar stroke defined clinicoradiologically more than other stroke subtypes but not simply by association with WMLs. This suggests that microbleeds and lacunar stroke have a similar microvascular abnormality. (Stroke. 2006;37:2633-2636.)

Key Words: brain imaging ■ brain infarction ■ hemosiderin ■ lacunar infarcts ■ leukokraurosis ■ microbleeds

Microbleeds are small (usually <5 mm in diameter\(^1\), low signal intensity areas seen on gradient echo (T2*-weighted) MRI corresponding with hemosiderin deposits in the cerebral microvascular perivascular spaces on pathology.

Microbleeds are common in patients with stroke, being associated with current intracerebral hemorrhagic (ICH),\(^3\) increased risk of future ICH,\(^4,5\) and with ischemic stroke.\(^4\) Whether or not there is an association with clinical lacunar infarction is unclear because studies used populations biased by risk factors (eg all hypertensive\(^6,7\)), had no nonlacunar stroke comparison group,\(^6\) only included patients with lacunar stroke seen on imaging\(^8\) or failed to make clear whether “lacunes” seen on imaging were symptomatic.\(^3,6–8\) Indeed, some lacunar infarcts seen on imaging were in completely healthy, never symptomatic individuals.\(^9\) Only two studies compared microbleeds with stroke subtype in patients with acute ischemic stroke and found microbleeds were more frequent in patients with a new lacunar stroke.\(^10,11\) However, these studies may have biased the diagnosis of stroke subtype by using a classification incorporating risk factors rather than pure neurologic findings.\(^12\)

If microbleeds are a manifestation of cerebral small vessel disease, they should be associated with both the clinical (ie lacunar stroke clinical syndrome) and imaging (ie recent small subcortical infarct in an area of brain relevant to the patient’s recent symptoms) features of cerebral small vessel disease. We assessed the frequency and associations of microbleeds in patients with mild stroke and healthy older subjects.

Subjects and Methods

We recruited patients presenting with stroke of lacunar, partial anterior or posterior circulation type,\(^13\) and healthy older community-dwelling subjects. All patients were examined by a trained stroke physician or geriatrician. The healthy older subjects, aged late 70s to early 80s, were recruited for a study of ageing.\(^14\) They had no history of cardiovascular or cerebrovascular disease, diabetes, or cancer (subjects were included if they had a history of hypertension but were well controlled on treatment).

All patients underwent MRI (the stroke patients at presentation, the healthy controls on recruitment) on a GE Signa LX 1.5-T (General Electric) clinical scanner equipped with a self-shielding gradient set and manufacturer-supplied “birdcage” quadrature head coil. The MRI examination consisted of axial T1-, weighted fast-spin

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echo; axial FLAIR fast spin-echo imaging; axial gradient echo (TR 625 ms, TE 15 ms, flip angle 20, field of view 24, slice thickness 5 mm, slice gap 1 mm, matrix 256×192, nex 2, phase field of view 0.75); and (in all except the ageing cohort) axial diffusion-weighted imaging (b=0 and 1000 s/mm²).

The images were coded by a consultant neuroradiologist blind to all other data and to any hypothesis about microbleeds. Recent and old infarcts and intracerebral hemorrhages were identified and then any infarcts on imaging were compared with the patient's clinical findings to determine whether the visible infarct was recently symptomatic or not. White matter lesions (WMLs) were coded using the Fazekas score. Microbleeds were defined on gradient echo images as homogeneous, hypointense rounded lesions of diameter located in the brain parenchyma. We counted the total number of microbleeds. Larger areas (5–10 mm diameter) of signal hypointensity in the brain parenchyma on gradient echo images were considered to be small old ICHs, although some have included lesions up to 10 mm in diameter as microbleeds. Symmetric areas of hypointensity likely to be the result of calcification or iron deposition in the globus pallidus were ignored as were flow voids in cortical sulci and hypointensities in any areas of cortex near the inner skull table, which were considered to be signal averaging from adjacent bone.

We examined for any association between microbleeds and (1) lacunar stroke defined clinically (“clinical syndrome”) and (2) according to the acute stroke lesion on imaging (“clinical and imaging syndrome”). We included the ICHs in the analyses according to their cortical/subcortical distribution and clinical syndrome because they were few in number and to avoid any bias that might occur by excluding patients whose hemorrhage was actually an infarct with hemorrhagic transformation. We used Fisher exact tests and χ² tests as specified in the text.

Results

We recruited 308 subjects, including 67 healthy older subjects (median age, 78 years; range, 74–80 years) and 241 patients with mild stroke (median age, 66 years; range, 19–89 years). There was no difference in the proportion of healthy controls receiving antihypertensive treatment (but with well-controlled blood pressure) and of lacunar or cortical stroke patients with a history of hypertension (42%, 45%, 47%, respectively, P not significant).

The clinically based diagnoses of the 241 stroke patients were 67 lacunar syndromes, 109 partial anterior circulation syndromes, 41 posterior circulation syndromes, and 84 uncertain (see Table 1). Microbleeds were classified according to their cortical/subcortical distribution and clinical syndrome. The number of microbleeds per subject ranged from 0 to 15. The majority of microbleeds were of cortical/subcortical distribution (100% of lacunar syndromes, 91% of PACS, 100% of posterior circulation syndromes, and 96% of uncertain). The chi-square test was used to evaluate the association between microbleeds and clinical and imaging stroke syndromes (see Table 2). There was a significant association between microbleeds and lacunar or cortical ischemic stroke defined radiologically only (P=0.016) and defined with combined clinical and radiologic data (P=0.03, χ² test). The numbers on the bars are the number of patients.

Clinical Stroke Syndrome and Recent Lesion on Imaging

<table>
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<tr>
<th>Clinical Syndrome</th>
<th>Cortical</th>
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<th>Posterior Circulation</th>
<th>Intracerebral Hemorrhage*</th>
<th>No Visible Relevant Lesion</th>
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<td>Uncertain</td>
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<td>2</td>
<td>0</td>
<td>15</td>
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</tbody>
</table>

*Note all intracerebral hemorrhages were in an appropriate distribution for the clinical syndrome caused.

Figure 1. The association between microbleeds and lacunar or cortical ischemic stroke (A) defined radiologically only (P = 0.016) (whether small intracerebral hemorrhage included or not), (B) defined with combined clinical and radiologic data (P = 0.03, χ² test). The numbers on the bars are the number of patients.
24 of uncertain syndrome type (Table). The imaging findings were 55 cortical infarcts, 66 subcortical (lacunar) infarcts, 16 brain stem/cerebellar infarcts, 19 ICHs, and 85 with no definite stroke lesion. All the ICHs were appropriate to the clinical syndrome (Table). The final combined clinical imaging diagnoses were 92 (38%) cortical strokes, 92 (38%) lacunar strokes, 42 (18%) brainstem or cerebellar strokes, and 15 (6%) of uncertain subtype.

Overall, 54 of 308 (17%) subjects had one or more microbleeds, ranging from six of 67 (9%) of healthy older subjects to 47 of 241 (20%) of patients with stroke. Microbleeds were more frequent among patients with lacunar stroke than those with cortical stroke whether defined using the combined clinicoradiologic information or just radiologically (Figure 1) but not if only defined on the clinical syndrome. Using the clinicoradiologic definition, 24 of 92 (26%) patients with lacunar stroke had microbleeds compared with 12 of 92 (13%) with cortical strokes (P=0.03, χ² test). The results were similar for the radiologic definition and whether the patients with ICH were included or excluded. Of the 19 patients with ICH, all except one had either microbleeds or small hematomas (5–10 mm in diameter).

There was no difference in the median deep white matter or periventricular WML scores between the patients with stroke and the healthy older subjects (median periventricular and deep WML scores =1 for both groups) or in the proportion in each group with high lesion scores (deep white matter—15% of healthy older subjects and 31% of stroke patients had a score of 2 or 3, χ² test for trend P=0.7). There was no statistically significant difference in WML scores between lacunar and cortical infarct patients (deep WML lesion scores 2 or 3—41% versus 30%; periventricular lesion scores 2 or 3—57% versus 46%, lacunar versus cortical infarction, respectively, χ² test for trend P=0.3).

Microbleeds were more frequent among those with higher WML scores (Figure 2): 19 of 34 (54%) patients with a Fazekas deep white matter score of 3 had microbleeds compared with only four of 47 (8%) patients with a Fazekas score of zero (P<0.0001, χ² test for trend). A similar pattern was observed for the association between microbleeds and the Fazekas periventricular WML score (P<0.0001, χ² test for trend).

Discussion

Microbleeds are associated with the clinicoradiologic syndrome of lacunar ischemic stroke more than other ischemic stroke subtypes. We were careful to ensure that we were not just studying asymptomatic lacunes of uncertain significance found on imaging, but true lacunar stroke, that the comparison of lacunar and cortical stroke subtypes was not confounded by the misclassification of stroke subtype that would occur with just the clinical features or biased by use of risk factor-based subtype definitions.

We have confirmed that microbleeds are associated with WMLs both in periventricular and deep white matter. However, this was not just because the lacunar strokes had more WMLs, as the difference in median WML scores, and in the proportion of patients with high WML scores between pa-
tients with lacunar and cortical ischemic stroke was not significant.

The frequency of microbleeds in our patients with stroke and healthy older subjects was similar to that reported previously.¹,² The very high frequencies reported in some previous studies of stroke (eg, 78%) may reflect bias in patient selection (eg, only including subjects with hypertension or hemorrhagic stroke).

The limitations of this study include the imperfect match of median age between the healthy older subjects and the patients with stroke. Some patients had recurrent strokes, although most patients had first strokes. We did not have detailed vascular risk factor and treatment data, but there was no difference in the proportion of healthy controls with well-controlled blood pressure on antihypertensive treatment and the proportion of patients with stroke with a history of hypertension.

Why should microbleeds be associated with lacunar stroke? Much lacunar ischemic stroke may result from insidious damage to the cerebral microvessel walls leading to increased cerebral microvascular permeability and consequent perivascular tissue damage.¹⁷ WMLs may result from a similar process, although both WMLs and lacunar infarction are generally considered to be “ischemic.” The association between microbleeds and lacunar stroke suggests that they may share a common pathophysiological mechanism involving increased permeability of the cerebral microvessels. Further study should be directed at improved understanding of the mechanism of lacunar stroke, WMLs, and microbleeds and the role of insidious cerebral microvascular endothelial damage.

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**Disclosures**
None.

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