Cerebral Microhemorrhages Predict New Disabling or Fatal Strokes in Patients With Acute Ischemic Stroke or Transient Ischemic Attack

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Background and Purpose—Cerebral microhemorrhages (MHs) are common among patients presenting with acute ischemic stroke and may predict both subsequent ischemic and hemorrhagic strokes.

Methods—We prospectively studied patients with and without MHs presenting within 12 hours of their ischemic stroke or transient ischemic attack (TIA). A magnetic resonance (MR) scan was performed within 24 hours of symptom(s) onset. The primary outcome was disabling or fatal stroke at 18 months.

Results—An MR scan was done in 236 patients with acute ischemic stroke or TIA. Forty-five (19.1%) patients had an MH on a baseline MR scan. Patients with MHs were 2.8× (10.8% versus 4.0%; $P=0.036$) more likely to have a subsequent disabling or fatal stroke than patients without an MH. The risk of symptomatic intracerebral hemorrhage was not statistically significant among MH and non-MH patients (3.3% versus 0.8%; $P=0.31$).

Conclusions—The presence of cerebral MH(s) in patients with acute ischemic stroke or TIA predicts recurrent disabling and fatal strokes. This risk is mainly assumed by recurrent ischemic strokes. **(*Stroke*. 2006;37:911-914.)**

Key Words: cerebral infarction ■ intracerebral hemorrhage ■ magnetic resonance imaging

The prevalence of microhemorrhage (MH) varies between 18% and 62% in patients with acute ischemic stroke.[1–3] MH may be a risk factor of subsequent intracerebral hemorrhage (ICH) and ischemic stroke among patients presenting with acute ischemic stroke.[3–6]

The aim of our study was to determine the risk of disabling or fatal stroke at 18 months in patients presenting with acute stroke or transient ischemic attack (TIA), with and without MH on magnetic resonance (MR).

Patients and Methods

Patient Selection

The current study represents a subgroup analysis from a peer-reviewed, ongoing, prospective cohort study evaluating neurovascular imaging techniques (MR, computed tomography [CT], and transcranial Doppler) for predicting clinical outcome and recurrent events in patients presenting early after ischemic stroke or TIA, the VISION study (Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischemic eveNts), of which some results were published previously.[7] Patients were eligible for VISION if they had an acute ischemic stroke or TIA (speech or motor) within the previous 12 hours and had a premorbid modified Rankin Scale (mRS)[8] score ≤3. To exclude patients with other neurological diagnoses (migraine, seizure, etc), only TIA patients with symptoms consisting of aphasia or hemiparesis lasting >5 minutes were included. Patients with persisting neurological symptoms compatible with ischemic stroke were eligible, even if these symptoms were not aphasia or hemiparesis. Exclusion criteria were: CT scan evidence of tumor or hemorrhage, classic migraine features (fortification spectra, typical sensory march), hypoglycemia (serum glucose <3 mmol/L), and serious comorbid illness with an unlikely chance of 3-month survival. Baseline demographic and clinical data were prospectively collected. All participants provided written informed consent. If patients had an impaired consciousness, a surrogate's consent was obtained. This study was approved by the local ethics review committee.

Imaging

MRI was performed as soon as possible and within 24 hours of symptom(s) onset. MRI studies were done with a 3-T MRI system (Signa; GE Medical Systems) equipped with high-speed gradients (40-mT/m peak strength; 184 μs rise time). All imaging was performed using a standard quadrature head coil. The protocol included sagittal, axial, and coronal T1 (3-Plane; 2D; localizer; echo time [TE]=1.7 ms; repetition time [TR]=53.5 ms; flip angle 30°; field of view [FOV]=22×22 cm; PhaseFov=1.0; 256×128 acquisition matrix [reconstructed to 256×256]; slice thickness/gap=5.0 mm/2.0 mm; 5 slices per direction [axial, sagittal, and coronal]; acquisition time=0 minutes 22 s), axial T2 (oblique axial; flip angle=160°; TE=102 ms; TR=4000 ms; FOV=24×18 cm; PhaseFov=0.75; 512×256 acquisition matrix [recon-

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structed to 512×512]; receiver bandwidth ±31.25 kHz; slice thickness/gap=5.0 mm/2.0 mm; 19 slices; acquisition time 2 minutes 16 seconds); axial fluid-attenuated inversion recovery (FLAIR; oblique axial; flip angle=160°; TE=147 ms; TR 9000 ms; FOV=24×24 cm; PhaseFov=1.0; 256×192 acquisition matrix [reconstructed to 256×256]; receiver bandwidth ±15.63 kHz; slice thickness/gap=5.0 mm/2.0 mm; 19 slices; acquisition time=3 minutes 0 s), 3D time of flight-nonenhanced and contrast-enhanced MR angiography (axial, 3D, TE=3.3 ms; TR=24 ms; flip angle=15°; FOV=24×14.4 cm; PhaseFov=0.6; 256×192 acquisition matrix [reconstructed to 512×512]; receiver bandwidth ±12.5 kHz; slice thickness=2.0 mm; 32 slices per slab; 2 slabs acquired; acquisition time=3 minutes 11 seconds), diffusion-weighted imaging (b=1000; oblique axial; TE=73.2 ms; TR=7000 ms; FOV=32×19.2 cm; PhaseFov=0.6; 192×192 acquisition matrix reconstructed to 256×256; acquisition time of 56 s, receiver bandwidth ±154 kHz; slice thickness/gap=5.0 mm/2.0 mm, 19 slices), gadolinium bolus-tracking perfusion-weighted echo-planar imaging (PW EPI; oblique axial; flip angle=45°; TE=45 ms; TR=1850 ms; FOV=32×19.2 cm; PhaseFov=0.6; 160×160 acquisition matrix [reconstructed to 256×256]; receiver bandwidth ±156.25 kHz; slice thickness/gap=5.0 mm/2.0 mm; 19 slices; acquisition time=1 minute 18 seconds) or gradient echo (GRE) sequences (oblique axial; TE=20 ms; TR=500 ms; flip angle of 18°; FOV=24×24 cm; PhaseFov=0.6; slice thisckness/gap=5.0/2.0 mm; 19 slices; receiver bandwidth ±20.83 kHz; 256×224 acquisition matrix; acquisition time of 1 minute 8 s). GRE sequences were not done routinely before December 2003, but PW EPI was already included in the protocol. All scans were reviewed from a designated work station by a neuroradiologist with expertise in stroke imaging who was blinded to the clinical data. A stroke neurologist blinded to clinical data also reviewed all CT scans and MRI. MHs were defined as small regions of hypointense signal on GRE sequences or on the first 12 T2* PW EPI images obtained before gadolinium contrast arrival. Subsequent perfusion-weighted images were not considered for the identification of MHs. Symmetric signal loss in the globus pallidum was interpreted as calcification. All head CT scan were also reviewed to exclude basal ganglia calcifications. Circular flow void artifacts in the sulci or surface of the brain were interpreted as attributable to blood vessels. White matter disease (leukoaraiosis) was classified as absent, punctate, early confluent, or confluent abnormalities on FLAIR sequences.[9,10] Patients were classified as having MHs absent or present.

Patient Outcomes

Each patient had a complete neurological evaluation including a National Institutes of Health Stroke Scale (NIHSS)[11] score and an mRS score at baseline and at 3 months. The index event was diagnosed as a stroke if the neurological symptoms lasted ≥24 hours and as a TIA if they were of shorter duration. At 3 months, the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[12] classification was used to determine the stroke and TIA etiology. Patients were managed according to best medical care and received secondary prevention as judged appropriate by the treating physician. At 6 months and every 6 months thereafter, the Questionnaire for Verifying Stroke-Free Status (QVSFS)[13] was completed by phone. Patients with positive answers to the QVSFS were assessed in person. A stroke was judged disabling when the mRS score was ≥3.

Statistical Analysis

The primary composite outcome for the present study was disabling or fatal stroke at 18 months after the index event. Secondary outcomes were all strokes and death. The 18-month risks of outcome were derived from product-limit estimates of event-free survival using Cox proportional hazards regression modeling. Cox modeling was used to adjust for differences in patient characteristics between those with and without MH when deriving adjusted risk estimates and for generating predicted event-free survival curves. Differences between proportions were assessed using a χ^2 test.

Results

An MR scan was prospectively completed in 248 patients from April 30, 2002, to April 29, 2004. Twelve patients were excluded from analysis because of a nonvascular diagnosis. The median follow-up was 14 months (1 to 732 days). Six (2.5%) patients were lost to follow-up. A total of 155 (65.7%) patients had a diagnosis of stroke and 81 (34.3%) of TIA at baseline. Most strokes were in the anterior circulation (125 of 155; 80.6%). Forty-five patients (19.1%) had MH at baseline. Diffusion-weighted imaging lesion was seen in 133 patients with stroke (85.8%) and 37 patients with TIA (45.7%; P=0.0001). Old age, diabetes, confluent white matter disease, and hypertension were seen more frequently among MH subjects (Table 1). Forty-three (95.6%) patients with MH and 184 (96%) non-MH patients received antithrombotics at discharge.

From the univariate analyses, patients with a MH were 4.4× more likely to have a disabling or fatal stroke within 18 months of their ischemic symptoms than patients without an

TABLE 1. Characteristics of Patients According to Presence and Absence of MH(s)

	Percentage of Group		
	Present (n=45)	Absent (n=191)	*P* Value
Age >75 years	68.9	39.8	<0.001
Male	62.2	53.4	0.28
NIHSS score >5	33.3	27.8	0.46
Received r-tPA	17.8	17.3	0.94
Antiplatelet agent at baseline	33.3	21.5	0.09
Systolic blood pressure >160 mm Hg	40.0	40.3	0.97
Diastolic blood pressure >90 mm Hg	37.8	30.9	0.37
Blood glucose >7 mmol/L	33.3	28.3	0.50
History of			
Hypertension	80.0	55.5	0.003
Diabetes mellitus	28.9	13.6	0.01
Ischemic heart disease	15.6	16.7	0.85
Stroke	28.9	22.0	0.32
Atrial fibrillation	20.0	17.8	0.38
Confluent white matter disease	68.9	30.4	<0.001
Etiology			
Small vessel disease	20.0	12.6	0.20
Large artery disease	17.8	23.0	0.44
Cardioembolic	26.7	22.5	0.55
Other determined etiology	0	4.7	0.14
Undertermined	35.5	37.2	0.84
DWI lesions	82.2	69.6	0.09
Symptoms to MR imaging >12 hours*	42.2	37.2	0.53

*Mean (SD) time from symptoms to MR: 10.9 (7.2) and 11.1 (9.0) hours, respectively.

r-tPA indicates recombinant tissue plasminogen activator.

TABLE 2. Eighteen-Month Risk (%) of Outcome Events and Hazard Ratios (HRs) by Presence and Absence of MHs

Outcome Event	Present (n=45)	Absent (n=191)	HR	95% CI HR	*P* Value HR
Disabling or fatal stroke					
Crude	22.8	5.7	4.4	1.8 to 11.2	0.002
Adjusted	10.8	4.0	2.8	1.1 to 7.3	0.036
All stroke*					
Crude	22.8	9.5	2.6	1.1 to 6.0	0.023
Adjusted	11.3	7.5	1.5	0.7 to 3.6	0.322
Death from any cause					
Crude	27.6	7.0	4.4	1.9 to 10.7	<0.001
Adjusted	16.5	5.6	3.1	1.2 to 7.8	0.015

Crude product-limit estimates of the event-free survival from Cox proportional hazards regression model. Risk estimates from Cox proportional hazards regression model adjusted for age and presence of confluent white matter disease.

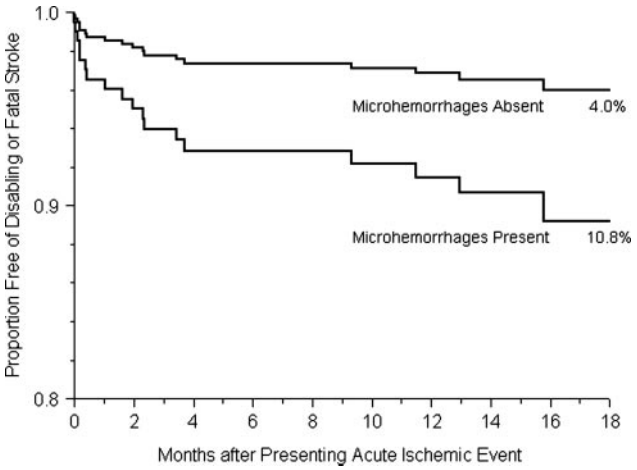
P value for testing the statistical significance of the HR.

*The ICH rate was 3.3% vs 0.8% in the MHs present and MHs absent groups, respectively (*P* value=0.31). The risk of ischemic stroke was 20.3% and 8.7%, respectively (*P* value=0.039).

MH (Table 2). Stroke severity (NIHSS), stroke subtype, antithrombotic therapy, hypertension, diabetes, and past medical history did not influence outcomes. Age and presence of confluent white matter disease were the only characteristics identified as confounding factors. Even after adjustment for both of these factors, patients with a MH were 2.8× more likely to have a subsequent disabling or fatal stroke (95% CI, 1.1 to 7.3; *P*=0.036; Table 2; Figure).

Ten patients with MH died: 7 new strokes, 1 congestive heart failure, and 2 severe pneumonias. The causes of deaths were similar among non-MH patients: 6 new strokes, 3 pneumonias, and 1 lung cancer.

A majority of new strokes were ischemic: 85.7% (6 of 7) and 94.1% (16 of 17) for the MH and non-MH groups, respectively. Only 1 symptomatic cerebral hemorrhage occurred in each group, including 1 patient with a single MH patient who died after thrombolysis.



Freedom from disabling or fatal stroke curves for patients with and without MH(s), adjusted for age and presence of white matter disease. The adjusted 18-month risks of disabling or fatal stroke are shown as percentages on the right-hand side of the curves.

Discussion

We showed that the presence of MH is a risk factor for a subsequent disabling or fatal stroke.

In a previous study, the presence of multiple MH predicted recurrence of both ischemic stroke and ICH, but a control group without MH was not used for comparison.[6] Our study is the first to show that patients presenting with an ischemic stroke or TIA and an MH are more likely to have a recurrent disabling or fatal stroke.

Most recurrent strokes were of ischemic origin. It is possible that some MHs represent hemorrhagic transformation of previous ischemic stroke or that MHs reflect vessel fragility, predisposing to subsequent endothelial instability and stroke.

There is a concern among physicians that antithrombotics could be harmful to MH patients.[14] This concern may be overstated. An increased risk of ICH (9.3%) was shown previously in patients with ischemic stroke and MH.[4] The population studied was Asian and could be more prone to ICH.[15] Another group found a 2.9% rate of ICH at follow-up in patients with MH at baseline.[3] The population studied was heterogenous; some patients had previous ischemic stroke or ICH, whereas a majority had no history of either.

Our study has some limitations. First, 55.6% of the MH patients had a solitary lesion. The study was not designed to analyze outcomes according to the number of MHs; too few patients with MHs prevented us from doing a post hoc analysis of outcomes in single versus multiple MHs. Meanwhile, a conservative attitude with antithrombotics is appropriate in patients with numerous MHs. Second, a larger number of patients and a longer follow-up may be required to find a significant increase of symptomatic ICH among MH patients. Third, no patient with or without MHs had previous symptomatic ICH in our study, and these patients may be at higher risk of recurrent ICH. Fourth, although some used EPI for the diagnosis of MHs, it may be less sensitive to MHs than GRE.[16] Contrary to others, we used a 3T MRI. and although it should be more sensitive than a 1.5-T MR for the presence of MH, this remains unproven.

In summary, we showed that the presence of MH is a predictor of subsequent disabling or fatal stroke in a population of ischemic stroke and TIA patients.

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