Cavitation After Acute Symptomatic Lacunar Stroke Depends on Time, Location, and MRI Sequence

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Background and Purpose—Definitions for chronic lacunar infarcts vary. Recent retrospective studies suggest that many acute lacunar strokes do not develop a cavitated appearance. We determined the characteristics of acute lacunar infarcts on follow-up MRI in consecutive patients participating in prospective research studies.

Methods—Patients with acute lacunar infarction on diffusion-weighted imaging were selected from 3 prospective cohort studies of minor stroke imaged within 24 hours of onset. Follow-up MRI was performed at 30 days (VISION study, n=21) or 90 days (VISION-2 and CATCH studies, n=34). Evidence of cavitation on MRI was rated separately on fluid-attenuated inversion recovery, T1, and T2 sequences by 2 independent study physicians; discrepant readings were resolved by consensus.

Results—Probable or definite cavitation on any sequence was more common at 90 days compared with 30 days (P<0.001 for all sequences). At 90 days, evidence of cavitation was seen on at least 1 sequence in 33 of 34 patients (97%). The T1-weighted sequence was most sensitive to the presence of cavitation (94% at 90 days). By contrast, the fluid-attenuated inversion recovery sequence frequently failed to show evidence of cavitation in the brain stem or thalamus (only 10 of 18 [56%] showed cavitation).

Conclusions—MRI scanning at 90 days with T1-weighted imaging reveals evidence of cavitation in nearly all cases of acute lacunar infarction. By contrast, reliance on fluid-attenuated inversion recovery alone will miss many cavitated lesions in the thalamus and brain stem. These factors should be taken into account in the development of standardized criteria for lacunar infarction on MRI. (Stroke. 2012;43:1837-1842.)

Key Words: acute stroke ■ lacunar infarcts ■ lacunes ■ magnetic resonance imaging

Lacunar stroke was first described as a clinicopathological syndrome by Marie1 and as a major cause of clinical stroke syndromes by Fisher.2 Pathological definitions of lacunar lesions are variable but typically require a subcortical lesion with complete or partial cavitation with maximum diameter 15 mm or 20 mm3–5 corresponding to a “Type I” lacune according to a classification system proposed by Poirier and Derouesse.4 Likewise, MRI and CT definitions of lacunes are also variable but typically require the identification of a central cavity with cerebrospinal fluid-like signal intensity.6–9 The identification of chronic lacunar lesions has taken on major importance because of multiple MRI studies showing that “silent” lacunes, in the absence of clinical stroke, are strongly associated with cognitive impairment and risk of stroke and dementia.8–10

Acute symptomatic lacunar stroke provides a prototypical model of lacunar lesion evolution because it allows precise identification of the time of onset of the lesion, its location, and the clinical mechanism (that is, infarction). Surprisingly, a recent study suggested that the majority of symptomatic lacunar infarctions do not evolve into a cavitated appearance on MRI but rather evolve into a nonspecific white matter hyperintensity.11 This finding, if confirmed, has major implications for the diagnosis and classification of cerebral small vessel disease and vascular cognitive impairment. Epidemiological studies have typically classified lacunar lesions separately from white matter lesions (WMLs) or subcortical gray matter T2 hyperintensities to investigate risk factors and consequences of these lesions.8–10,12 If WML and lacunar infarction are indeed less distinct than orig-
nally conceived, then the epidemiological findings may be biased by misclassification.

In this study, we used data from 3 prospective longitudinal MRI research studies of stroke to investigate the process of lacunar lesion evolution. Our objective was to determine the proportion of acute lacunar infarcts that evolved into a cavitated appearance on follow-up MRI and to identify the determinants of MRI-defined cavitation, including MRI sequence type, lesion location, and patient characteristics.

Methods

We identified participants with acute lacunar stroke from 3 prospective studies of ischemic stroke and transient ischemic attack with MRI < 24 hours after onset: Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischemic eveNts (VISION study; enrolling patients with any National Institutes of Health Stroke Scale severity).

Evolution of magnetic resonance imaging as a potential surrogate end point for future stroke intervention trials when compared to clinical Outcomes in Nondisabling minor stroke and TIA (VISION-2; enrolling patients with National Institutes of Health Stroke Scale ≤ 5), and CT And MRI in the Triage of TIA and minor Cerebrovascular events to identify High risk patients (CATCH; enrolling patients with National Institutes of Health Stroke Scale ≤ 3). Full study inclusion and exclusion criteria are provided in the online-only Data Supplement.

All 3 studies included a baseline MRI done within 24 hours and either a 30-day (VISION) or 90-day (VISION-2 and CATCH) follow-up MRI. Baseline demographics, details of the clinical assessment, and stroke type were prospectively recorded in study case report forms.

Eligibility for this study was based on an MRI-confirmed clinical diagnosis of acute lacunar infarction, defined as: 1) baseline MRI showing restricted diffusion in a deep brain region, corresponding to the presumed territory of a single penetrating artery; 2) maximum diameter ≤ 25 mm; 3) absence of multiple lesions that could suggest embolic infarctions; and 4) a confirmatory clinical improvement of acute lacunar infarction based on all neuroimaging and clinical information prospectively recorded as a diagnosis of acute lacunar stroke (CATCH) or when compared to clinical Outcomes in Nondisabling minor stroke and TIA (VISION-2).

Results

Among 67 participants with a clinical lacunar syndrome, 60 (90%) had evidence of an acute lacunar infarct on diffusion-weighted imaging. Among these 60 eligible participants, 5 (8%) were excluded because there was no follow-up scan. This left 55 participants for analysis. Mean age was 65 years (SD 10.7) and 65% were male. The median baseline diffusion-weighted imaging lesion diameter was 13 mm (interquartile range, 9–18 mm). The acute infarct was visible on FLAIR in 42 of 55 patients (76%); median diameter was 10 mm (interquartile range, 7–16 mm). The acute lacunar infarct was located in the lobar white matter (not involving the basal ganglia or internal capsule) in 12 (22%), internal capsule in 11 (20%), globus pallidus or striatum with adjacent white matter in 6 (11%), thalamus in 9 (16%), and brain stem in 17 (31%) patients. Other characteristics of the study population are shown in Table 1.

All patients had MRI FLAIR at follow-up but some patients were missing other MR sequences: 3 were missing the T1-weighted sequence, 4 were missing the T2-weighted sequence, and 15 were missing the gradient-recalled echo sequence. A hyperintensity was visible on the follow-up FLAIR in 52 of 55 patients (95%). Probable or definite cavitation was less frequently present in the patients scanned at 30 days compared with 90 days (Table 2). At 30 days, cavitation was seen in 4 of 20 (25%) on FLAIR, 4 of 20 (25%) on T2-weighted, and 10 of 19 (53%) on T1-weighted sequences. By comparison, at 90 days, cavitation was seen on FLAIR in 52 of 55 patients (95%) and on T1-weighted in 30 of 32 (94%) patients.

In Table 1 the proportion with cavitation at 90 days was higher on the T1-weighted sequence than FLAIR (chi-square = 26.0, 1 df, P < 0.001 for all comparisons with 30 days). Cavitation was seen in at least 1 of the 3 sequences at 90 days in 33 of 34 (97%). The proportion with cavitation at 90 days was higher on the T1-weighted sequence than FLAIR (P = 0.01), driven by a lack of cavitation on the FLAIR sequence compared with the T1-weighted sequence in brain stem and thalamic lacunes (16 of 18...
Timing of Follow-Up

Table 2. Frequency of Cavitation on MRI Sequences in Patients Scanned at Either 30 Days or 90 Days

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N=55)</th>
<th>30 d</th>
<th>90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.9±10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (66%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI diameter, mm</td>
<td>13 [9, 18]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLAIR diameter, mm</td>
<td>10 [7, 16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI volume, cm³</td>
<td>0.7 [0.3, 1.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLAIR volume, cm³</td>
<td>0.7 [0.3, 1.0]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLAIR diameter, follow-up</td>
<td>11 [8, 17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLAIR volume, follow-up</td>
<td>0.8 [0.4, 1.8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy scale score</td>
<td>1 [1, 2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas WML score</td>
<td>2 [2, 4]</td>
<td></td>
<td></td>
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<tr>
<td>Acute lacunar infarct location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia/internal capsule</td>
<td>17 (31%)</td>
<td></td>
<td></td>
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<tr>
<td>Subcortical white matter</td>
<td>12 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>9 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>17 (31%)</td>
<td></td>
<td></td>
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<tr>
<td>Chronic lacunes</td>
<td>24 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbleeds</td>
<td>14 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>11 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>16 (62%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (8%)</td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean±standard deviation or median [25th percentile, 75th percentile] unless otherwise noted.

DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; WML, white matter lesion.

showed cavitation on the T1-weighted sequence but only 10 of 18 showed cavitation on FLAIR.

Because the data suggested that the process of cavitation is incomplete at 30 days, we restricted analyses of predictors of FLAIR cavitation to the 34 patients with 90-day scans. Characteristics of participants with or without cavitation are shown in Table 3; representative case examples are shown in Figures 1 and 2. Baseline lesion diameter or volume was not related to FLAIR cavitation, but smaller follow-up FLAIR volume was associated with lack of FLAIR cavitation (P=0.01). Lesions without FLAIR cavitation were more likely to be located in the thalamus or brain stem (P=0.005) and were more likely to be in patients with lower Fazekas WML scores (P=0.009). Compared with basal ganglia and white matter lacunar infarcts, thalamic and brain stem lacunar infarcts were smaller at follow-up (median 0.23 cm³ versus 1.1 cm³; P<0.001) and more likely seen in patients with lower WML scores (median Fazekas score 2 versus 3.5; P=0.02).

Discussion

In this study we found that radiographic cavitation after acute lacunar infarction is incomplete at 30 days but almost always present at 90 days (33 of 34 patients) when evaluated using a comprehensive MRI acquisition. However, we found that the sensitivity of FLAIR for cavitation was considerably lower than for T1-weighted sequences and that the probability of FLAIR cavitation varied by lesion location, lesion evolution, and severity of WML.
Our findings contrast with 2 recently published studies of the evolution of acute lacunar stroke on CT or MRI. In 1 study, only 25 of 90 patients (28%) showed evidence of evolution into a cavitated lesion, including only 14 of 33 (42%) of patients with an MRI-confirmed acute infarct and a follow-up MRI. Longer time to follow-up was associated with an increased likelihood of cavitation (median time 228 days in patients with cavitation versus 72 days in patients without cavitation), similar to our study. In another study, cavitation was seen on 23 of 38 MRI (61%) and 50 of 70 CT (70%). There were some methodological limitations of these previous studies, however. The timing of follow-up ranged widely (6 days to >4 years) because follow-up was nonconsecutive and done for clinical indications, raising the possibility of bias. Follow-up was available in only 75 of 250 consecutive cases (30%) in the study that reported the rate of follow-up. The exact sequences and parameters used to determine cavitation in each individual were not given. A reliance on FLAIR alone could partially explain the lower rate of apparent cavitation compared with our study, because we have demonstrated that FLAIR is significantly less sensitive than the T1-weighted sequence. Other methodological differences compared with our study include the retrospective designs, use of multiple 1.5-T scanners (compared with a single 3.0-T scanner in our study), enrollment in the subacute phase of stroke in some cases (median time to baseline imaging was 10–18 days in 1 study), and use of a clinical definition of lacunar stroke with normal MRI in 23% of the patients in 1 of the studies. Although MRI is not perfectly sensitive for lacunar stroke, the inclusion of cases without MRI confirmation may be problematic given that CT is much less sensitive than MRI and the specificity of the clinical diagnosis of lacunar stroke is poor. By contrast, in our study we were able to use data from 3 prospective longitudinal studies with MRI confirmation of acute lacunar stroke in the acute period followed by study-mandated follow-up.

Despite evidence of cavitation on the T1-weighted sequence, the FLAIR sequence frequently failed to show evidence of cavitation. One possible reason is that the slice thickness was higher on the FLAIR than the T1-weighted sequence, which may have led to more partial volume averaging with normal tissue. However, we identified other characteristics associated with the lack of FLAIR cavitation. Although all of the basal ganglia and white matter lacunar infarcts showed evidence of cavitation on FLAIR, only 10 of 18 thalamic and brain stem infarcts showed evidence of cavitation on FLAIR. The lack of apparent cavitation on FLAIR, despite clear evidence of cavitation on other sequences, has previously been observed in thalamic lacunes. The partial or absent central hypointensity on FLAIR, despite clear hypointensity on the T1-weighted sequence (Figure 2), probably reflects incomplete suppression of the cavity fluid by the inversion pulse. Lack of fluid suppression could potentially result from a difference in the T1 relaxation time of the intralacunar fluid compared with CSF or lack of penetration of the radiofrequency pulse (dielectric effect). Thalamic and
brain stem lacunar infarcts were smaller at follow-up and occurred in patients with lower WML scores. WML may be associated with the appearance of cavitation on FLAIR because they reflect lack of tissue integrity, which promotes evolution into a larger lacunar lesion, which was also associated with a cavitated appearance on FLAIR. We failed to confirm a previous finding of greater likelihood of FLAIR lacunar infarct cavitation in the absence of diabetes. Only 2 patients (6%) had no cavitated appearance on the T1-weighted sequence when imaged at 90 days. In these 2 cases, the lacunar infarction may have been incomplete, corresponding to a Type Ib lacune in the modified version of the original small vessel disease classification system by Poirier and Desrouesne (in which the classic cavitated lacune is classified as Type Ia). A limitation of our study is that we do not have pathological correlation of our observed MRI findings. Previously published MRI pathology correlations have mainly focused on differentiating lacunes from Virchow-Robin spaces without comprehensively evaluating the appearance of lacunes across MRI sequences. There are some additional caveats that should be considered when interpreting our findings. The sample was small but well characterized. MRI sequences were reviewed simultaneously; therefore, the lesion appearance on 1 sequence might have biased the interpretation of other sequences. Our study design required a cohort with symptomatic acute lacunar infarction but 2 of the studies only enrolled patients with mild stroke severity; therefore, it is possible that the study findings may not be representative of either asymptomatic (silent) lacunar infarcts or more clinically severe larger lacunar infarcts if the pathogenesis is different. Silent lacunar infarcts likely differ in location and could differ in the severity of ischemia (possibly resulting in a higher proportion of incomplete Type Ib versus cavitated Type Ia infarcts). Acute lacunar infarction is presumed to be caused by vascular occlusion but other causative mechanisms for silent infarction may exist, including blood–brain barrier breakdown or inflammation. Furthermore, the pathogenesis may vary by location because subcortical incident lacunes frequently develop within existing WMH. However, incident silent lacunes cannot be detected acutely because the lesion is asymptomatic or minimally symptomatic; therefore, selecting patients with acute lacunar stroke remains the only practical way of identifying the radiological evolution of lacunar infarction from the acute to the chronic stage.

The main implication of our findings is that the sensitivity of MRI for detection of chronic lacunar infarction depends on the type of MRI sequences used and analyzed. This highlights the need for standards for acquiring, analyzing, and reporting MRI data relevant to cerebral small vessel disease. A reliance on FLAIR alone without whole-brain T1-weighted imaging, as may be done in clinical protocols, will have substantially lower sensitivity for identifying chronic lacunar infarcts and will misclassify many infarcts as either WML or subcortical gray matter T2 hyperintensities. Sensitivity of FLAIR is particularly poor in the thalamus, a critically
important region where small strategic infarctions are sufficient to cause vascular cognitive impairment. This has implications for both clinical care and research. Clinically, lack of recognition of chronic lacunar infarcts, including strategically located thalamic infarcts, may lead to underrecognition of vascular cognitive impairment. In research, misclassification of chronic lacunar infarction as WML or gray matter T2 hyperintensities will tend to obscure differences in pathogenesis, risk factors, and consequences of these lesion types. Furthermore, because the incidence and prevalence of chronic lacunar infarction will depend on the MRI acquisition protocol, it is critically important that the MRI acquisition methods be specified when reporting results. We recommend that high-resolution T1-weighted MRI with whole brain coverage be incorporated into clinical and research protocols for cerebrovascular disease to maximize sensitivity for chronic lacunar infarction and minimize misclassification of lacunar infarction as other lesions.

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Disclosures
None.

References
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