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Frequency of Subclinical Lacunar Infarcts in Ischemic Leukoaraiosis and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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BACKGROUND AND PURPOSE: Small vessel cerebrovascular disease is an important cause of vascular cognitive impairment. It is usually sporadic but also occurs secondary to the genetic disorder cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Recurrent lacunar stroke is a characteristic feature, although symptomatic events are relatively rare, making large numbers necessary for evaluation of potential therapies. Diffusion-weighted imaging is sensitive to acute ischemic lesions and differentiates them from chronic infarcts. Detection of asymptomatic lacunar infarcts with diffusion-weighted imaging is a potential surrogate marker for treatment trials. In this study, the frequency of asymptomatic new lesions in ischemic leukoaraiosis and CADASIL was determined as a step toward assessing the potential of this technique as a surrogate marker of disease activity.

METHODS: Fifty patients with sporadic small vessel disease and 19 patients with CADASIL underwent diffusion-weighted imaging. All had been asymptomatic for 3 months before imaging. Diffusion-weighted images were screened by two raters for new lesions; lesions were confirmed as recent by a visible reduction of diffusivity on the corresponding apparent diffusion coefficient maps.

RESULTS: Recent ischemic lesions were identified in four patients with sporadic small vessel disease (8.0%) and two patients with CADASIL (10.5%).

CONCLUSION: Asymptomatic new lesions are found in cases of sporadic small vessel disease and CADASIL. The frequency of new lesions suggests that this approach has a potential role as a surrogate marker in therapeutic trials that warrants further investigation.

Cerebral small vessel disease is an important cause of progressive cognitive impairment and a major contributor to vascular dementia (1). Typically, the neuropathology features a combination of focal lacunar infarcts and more diffuse axonal loss, demyelination, and gliosis (2). The coexistence of focal and diffuse abnormalities is reflected on conventional T2-weighted MR images by the combination of multiple,

discrete, focal lesions and more diffuse areas of hyperintensity or leukoaraiosis (3). Leukoaraiosis is a radiologic entity, and although cerebral small vessel disease is the most common underlying pathologic abnormality, similar appearances occasionally result from nonischemic mechanisms. The concept of "ischemic leukoaraiosis," which combines radiologically indicated leukoaraiosis with clinical lacunar stroke, has been used to define a more homogeneous group of patients in whom small vessel disease is likely to be well established as the principal underlying pathologic process (4). Pathologic and radiologic findings consistent with a combination of widespread white matter ischemia and recurrent lacunar infarction also occur in association with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a condition in which mutations of the *Notch 3* gene are associated with stroke-like episodes and cognitive decline (5, 6). The characteristic pathologic abnormalities consist of ac-

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TABLE 1: Clinical and radiologic findings in the two study groups

	Ischemic Leukoaraiosis (n = 50)	CADASIL (n = 19)
Clinical characteristics		
Age (yr \pm SD)	69.8 \pm 9.8 (range, 47–86)	47.3 \pm 12.2 (range, 21–69)
Males	32 (64%)	8 (42%)
Hypertension	40 (80%)	1 (5%)
Diabetes mellitus	6 (12%)	None
Anti-platelet therapy	46 (92%)	15 (79%)
Anti-coagulant therapy	None	2 (10%)
Global cognitive function		
MMSE score 28–30	25 (50%)	16 (84%)
MMSE score 24–27	14 (28%)	3 (16%)
MMSE score <24	7 (14%)	None
MR imaging findings		
Confluent changes (score of 3 on Fazekas scale)	43 (86%)	17 (90%)

Note.—CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MMSE, Mini-Mental State Examination.

cumulation of granular osmiophilic material and loss of medial smooth muscle cells within the walls of blood vessels (7). Although these changes are found in many tissues, the major clinical manifestations result from disease of the brain. Multiple lacunar infarctions co-exist with widespread demyelination, axonal loss, and gliosis. Diffuse involvement of the white matter and deep gray nuclei, with sparing of the subcortical U fibers and cortical gray matter, suggests involvement of a similar population of small penetrating arterioles that are implicated in sporadic ischemic leukoaraiosis. The presence of discrete focal lesions in many patients with both conditions suggests that recurrent lacunar infarction plays a role in progression of disease. However, symptomatic lesions are relatively rare and cognitive decline often occurs without overt symptoms.

Treatment options are currently limited for both ischemic leukoaraiosis and CADASIL. The rarity of symptomatic lacunar strokes is an important obstacle in evaluating new therapies; large sample sizes are likely to be required for treatment trials using clinical end points alone. Although clinical end points set the ultimate standard for definitive clinical trials, more sensitive surrogate markers would be useful in evaluating the efficacy of new treatments and selecting the most promising treatments for large trials. An analogy is provided by multiple sclerosis, for which detection of new lesions by contrast-enhanced MR imaging has been implemented as a surrogate marker of disease activity (8, 9) and has played an important role in developing new treatments. These lesions frequently are asymptomatic (8), but their detection on T2-weighted MR images predicts both clinical relapses and increases in disease burden (10, 11). New lesion detection has been incorporated into guidelines for disease monitoring in therapeutic trials in multiple sclerosis (9). Despite the emergence of potential new therapies that may limit cognitive decline, potential surrogate markers of disease activity remain relatively unexplored in small vessel disease.

Diffusion-weighted MR imaging provides a method for detecting recent ischemic lesions. Diffusion is reduced in an area of acute infarction, which is visible on diffusion-weighted images as an area of hyperintensity. Diffusivity is thought to remain reduced relative to normal values for 7 to 10 days after an acute event (12). Diffusion-weighted imaging provides excellent sensitivity for detecting symptomatic lacunar infarcts (13), and silent ischemia has been detected in asymptomatic patients with small vessel disease (13, 14). However, the usefulness of this technique as a surrogate marker will depend on the frequency with which asymptomatic lesions occur. One small study of 20 patients with preexisting vascular dementia and small vessel disease found asymptomatic lesions in 20% of the study participants (14), but it is not clear how these results apply to the wider population of patients with small vessel disease. Furthermore, the frequency of new ischemic lesions in patients with CADASIL has not previously been reported. With this study, we determined the frequency of asymptomatic new lesions, identified by diffusion-weighted imaging, in separate cohorts of patients with ischemic leukoaraiosis and CADASIL.

Methods

Patients

Fifty patients with ischemic leukoaraiosis and 19 patients with CADASIL underwent diffusion-weighted imaging at two centers. Of these, 37 patients with ischemic leukoaraiosis and 17 patients with CADASIL underwent imaging at King's College Hospital and 13 patients with ischemic leukoaraiosis and two patients with CADASIL underwent imaging on a similar MR imaging system at St. George's Hospital. Patients were identified from those attending a specialist cerebrovascular disease clinic supervised by one of the authors (H.S.M.) and through a national study to determine the prevalence of CADASIL in Great Britain. The characteristics of the patient groups are presented in Table 1. The study was approved by the local research ethics committee, and all participants provided informed consent.

Patients with ischemic leukoaraiosis. Ischemic leukoaraiosis was defined as the combination of radiologically indicated leukoaraiosis (diffuse T2 hyperintensity) and a history of a clinical lacunar syndrome (15). All participants had been assessed with Doppler sonography of the carotid arteries and MR imaging within 6 months of study entry. Exclusion criteria were carotid stenosis (>50%); cortical or large subcortical infarcts (>15 mm maximum diameter), considering that these infarcts often have a large vessel or embolic origin; evidence of cardiac or other embolic sources; and symptomatic stroke or transient ischemic attack during the 3 months preceding the study. Consecutive patients fulfilling these criteria who agreed to undergo MR imaging were recruited. Thirty-four patients from the ischemic leukoaraiosis group were screened for mutations causing CADASIL in exons 3, 4, 5, and 6 of the *Notch 3* gene. These exons harbor 90% of mutations in the British population, but screening was negative in all patients with ischemic leukoaraiosis who were tested. In all cases, MR images (T2-weighted or fluid-attenuated inversion recovery images) had been rated by using the Fazekas MR imaging rating scale (16).

Patients with CADASIL. For all patients with CADASIL, the diagnosis was confirmed by DNA sequencing and identification of characteristic mutations in the *Notch 3* gene (17). All had been previously symptomatic, with a duration of symptoms ranging from 1 to 24 years (mean \pm SD, 7.8 ± 5.9 years). Fourteen had experienced strokelike episodes in the past: a single episode in each of six patients, two episodes in each of two, and at least four episodes in each of six. However, all patients had been free of symptoms of stroke or transient ischemic attack for the 3 months preceding study entry. One patient had had a migraine during the 2 weeks before MR imaging that had been complicated by transient right-sided sensory symptoms and a transient fluent dysphasia and dysgraphia.

MR Imaging

MR imaging was performed on two similar 1.5-T GE Signa MR imaging units (General Electric Medical Systems, Milwaukee, WI). For the imaging unit used at King's College Hospital, axial diffusion-weighted images were acquired by using a spin-echo echo-planar imaging sequence (TR, 9 R-R intervals on ECG; TE, 121.1 ms; maximum strength of diffusion gradients, 22 mT/m; maximum b value, 1000 s/mm²). Fifteen to 18 near-axial 5-mm sections with 1-mm gaps provided coverage of supratentorial structures for all patients.

At St. George's Hospital, axial diffusion-weighted images were acquired by using a spin-echo echo-planar imaging sequence (2000/85 [TR/TE]; maximum strength of diffusion gradients, 22 mT/m; maximum b value, 1000 s/mm²). Twenty-two contiguous 5-mm sections provided coverage of supratentorial structures for all patients and variable coverage of infratentorial structures.

In both cases, diffusion-weighted images and apparent diffusion coefficient (ADC) maps corresponding to one-third of the trace of the diffusion tensor were generated by using in-house software. Isotropic diffusion-weighted images were generated; these images were weighted according to the ADC values averaged in all spatial directions so that they were independent of underlying fiber orientation and diffusional anisotropy. This is important because acquisition in a single spatial direction can make image interpretation difficult in anisotropic structures such as the corpus callosum. The diffusion-weighted images and ADC maps from the two imaging units were directly comparable; the diffusion sensitivity of each sequence (indicated by the maximum b factor of 1000 s/mm²) and the strength of diffusion-encoding gradients were identical. The sequences differed only in the scheme of gradient vector directions chosen. Although this does affect anisotropy measurements in diffusion tensor imaging, it has no significant effect on the values of ADC obtained (18). Corresponding echo-planar T2-weighted images were also obtained.

Image Analysis

Qualitative visual analysis: diffusion-weighted imaging, ADC mapping, and T2-weighted MR imaging. Diffusion-weighted images were reviewed by two experienced raters (P.M.R., H.S.M.). The images were randomized so that the raters were blinded to clinical category (ischemic leukoaraiosis versus CADASIL). Diffusion-weighted imaging provides the greatest sensitivity for detecting recent ischemia; in acute lesions, both reduced ADC values and increased T2-weighted signal intensity contribute to lesion conspicuity. However, false positive lesions may result from T2 changes alone, which is an effect described as *T2 shine-through* (19). To maximize sensitivity for recent ischemic lesions, both raters initially screened the diffusion-weighted images for hyperintensities. In all cases of diffusion-weighted imaging hyperintensity, each rater then reviewed the ADC maps and T2-weighted MR images. An area of diffusion-weighted imaging hyperintensity was classified as a recent ischemic lesion only if a corresponding reduction of ADC values compared with those of surrounding tissue was confidently identified on the ADC map.

In cases of disagreement or uncertainty, a consensus view was reached by reviewing all image types at a meeting of both raters. Consensus data are presented.

Quantitative measurements of mean diffusivity (regional ADC values). For all areas of hyperintensity identified by the raters, quantitative measurements of ADC were obtained. Diffusion-weighted images were displayed on a SUN Ultra 10 workstation by using the *Dispim* image display software (David Plummer, University College London). A semi-automated technique was used to outline lesions by using the "Contour" function. An operator placed a cursor at the edge of a visible lesion. The software, by using an algorithm based on local intensity thresholds, completed a region of interest around each lesion. These regions of interest were then transposed onto the ADC maps, and mean values of ADC within each region of interest were calculated.

Results

Frequency of New Lesions

Six recent ischemic lesions were identified in four patients with ischemic leukoaraiosis (8.0%) and two patients with CADASIL (10.5%). Examples of recent ischemic lesions are shown in Figure 1A and B. The clinical characteristics of the patients with recent ischemic lesions are presented in Table 2. In addition to the six recent ischemic lesions, 14 areas of hyperintensity in nine patients were selected by the raters from initial screening of diffusion-weighted images but were rejected by both raters as T2 shine-through effects when reviewing the ADC maps (Fig 1C). Diffusion-weighted imaging findings were negative for the patient with CADASIL who had a history of complex migraine during the 2 weeks preceding MR imaging.

Measurement of Mean Diffusivity (ADC Values)

ADC values were clearly reduced within all recent ischemic lesions, compared with values that have been obtained both in normal appearing white matter and regions of leukoaraiosis (20). Little overlap with ADC measurements occurred in areas of diffusion-weighted imaging hyperintensity classified as T2 shine-through. The mean ADC value (\pm SD) for the population of recent ischemic lesions was $0.70 \pm$

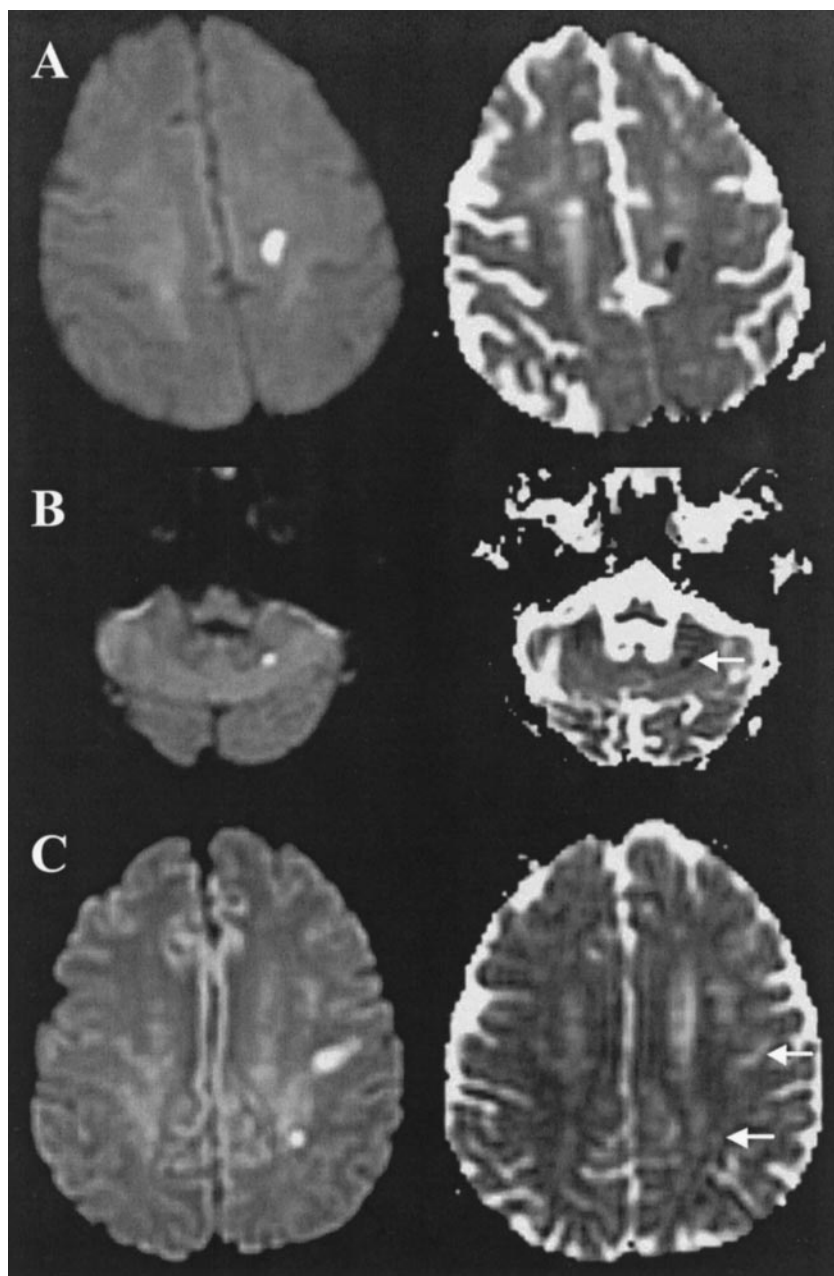


FIG 1. Examples of recent ischemic lesions and T2 shine-through effect. For recent lesions, high signal intensity is seen on the diffusion-weighted images (*left*), and corresponding reductions of diffusivity are seen on the ADC maps (*right*, *arrows*).

A, A recent asymptomatic ischemic lesion is seen in the left centrum semiovale in a patient with ischemic leukoaraiosis.

B, A recent asymptomatic ischemic lesion is seen in the left cerebellar hemisphere in a patient with CADASIL.

C, Two areas of hyperintensity are seen on the diffusion-weighted images of a different patient (*left*) and are found to correspond with increased ADC values (*right*, *arrows*), indicating that these are chronic lesions.

$0.12 \times 10^{-9} \text{ m}^2/\text{s}$, compared with $0.92 \pm 0.13 \times 10^{-9} \text{ m}^2/\text{s}$ for false positive regions of diffusion-weighted imaging hyperintensity ($P = .005$).

Discussion

This study showed that asymptomatic recent ischemic lesions can be identified in a substantial proportion of patients with ischemic leukoaraiosis and CADASIL. The prevalence of asymptomatic recent ischemic lesions was 8.0% in ischemic leukoaraiosis and 10.5% in CADASIL. These findings are important for two reasons. First, they provide an insight into the mechanisms of disease in ischemic leukoaraiosis and CADASIL and highlight a potential role of asymptomatic infarction in mediating insidious cognitive decline. The importance of this mechanism now

needs to be assessed in longitudinal studies. Second, this study showed that diffusion-weighted imaging detects new ischemic lesions with greater sensitivity than does clinical assessment alone, suggesting a possible role as a surrogate marker of disease activity.

Our findings extend those presented by Choi et al (14) to a broader population of patients with cerebral small vessel disease by including patients who are less severely affected and do not fit criteria for dementia. The earlier study examined 20 patients with subcortical vascular dementia and found asymptomatic lesions in four cases (20%). The higher prevalence found in the study by Choi et al may have occurred by chance because of the small sample size but, alternatively, could have occurred because of differences in the patient population. In the study presented by Choi et al, patients were selected on the basis of

TABLE 2: Clinical characteristics of patients with asymptomatic new lesions

Age (yr)/Gender	Clinical Details	Diffusion-weighted Imaging
75 M	1979, left hemiparesis, dysarthria; 1992, 1998, episodes of unexplained loss of consciousness, hypertension; no symptoms for 8 months before MR imaging; MMSE score, 29	Left centrum semiovale infarct
55 M	1995, right hemiparesis; 1999, right hemiparesis, dysarthria; no symptoms for 7 months before MR imaging; gait apraxia, pseudobulbar palsy, MMSE score, 25	Right frontal subcortical lacunar infarct
74 M	1991, right hemiparesis; 1998, episode of confusion; 1999, right hemiparesis and sensory loss (120 days before MR imaging); hypertension, smoker, MMSE score, 26	Left lentiform nucleus lacunar infarct
65 M	2001, right hemiparesis (97 days before MR imaging), hypertension; 1991, myocardial infarction, chronic renal failure; MMSE score, 30	Right lentiform nucleus lacunar infarct
53 M	CADASIL; 1980s, right hemisensory disturbance, migraine; 1999, encephalopathy; no symptoms for 10 months before MR imaging; MMSE score, 30	Left centrum semiovale infarct
49 M	CADASIL; multiple events affecting both hands (weakness, numbness), dysarthria; no symptoms for 4 months before MR imaging; MMSE score, 28	Left cerebellar hemisphere lacunar infarct

Note.—M indicates male; MMSE, Mini-Mental State Examination; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

preexisting dementia, which is an approach that is likely to select patients at the more severe end of the disease spectrum where ischemic events might be more frequent. Only seven patients in the present study had severe reductions in Mini-Mental State Examination scores consistent with a diagnosis of dementia. One possible end point for a clinical trial would be prevention of progression to dementia, and patients included in our study would fall into an appropriate target group for such a trial.

Our results also extend the findings of previous studies to patients with CADASIL, a genetic form of cerebral small vessel disease. The frequency of asymptomatic lacunar stroke in CADASIL has not previously been reported, but despite possible differences in pathogenesis, a similar prevalence of recent ischemic lesions was found. However, the prevalence rates in the two groups cannot readily be compared because the patients with CADASIL were younger and were less severely affected in terms of Mini-Mental State Examination scores. The patients with CADASIL with new lesions had Mini-Mental State Examination scores of 28 and 30, suggesting that new lesions can be detected early during the course of cognitive decline, which is when preventative therapies may be most effective.

Interestingly, diffusion-weighted imaging findings were negative for one patient with CADASIL who reported a history of complex migraine during the weeks preceding MR imaging. Migraine is a cardinal feature of CADASIL, but the pathophysiological basis is unknown. Migraine associated with CADASIL is often "complex" with prolonged focal deficits (including transient hemiparesis) that are unusual in the more typical form of migraine with aura. The boundary between complex migraine and transient ischemic attack is sometimes indistinct in this disease, which could reflect an ischemic basis for both manifestations. In this patient, it seems that the transient dys-

phasia was not the result of a new lacunar infarct, although a subtle, reversible episode of ischemia remains a possibility.

The pattern of radiologic abnormalities is not identical in ischemic leukoaraiosis and CADASIL. Hyperintensities of the temporal pole and external capsule are characteristic findings that are associated with CADASIL but are rarely encountered in association with sporadic ischemic leukoaraiosis (21, 22). No corresponding difference in the site of asymptomatic new lesions was identified in this study, and neither of the new lesions in patients with CADASIL was found in the temporal pole white matter or external capsule. It is possible that the anatomic distribution of lacunar infarcts is similar in the two conditions but that the pattern of more widespread, chronic ischemia differs, perhaps because of involvement of a population of vessels with a slightly larger caliber in CADASIL.

The properties possessed by good surrogate markers have been described previously in the context of cardiovascular disease (23). The first important property is that a surrogate marker should be easily measurable and sensitive to change. Detection of new lesions with diffusion-weighted imaging is a good technique according to this criterion, because new lesions are very conspicuous and are unlikely to be overlooked. In contrast, some new lesions are likely to go undetected by serial assessment of T2-weighted MR images, as has been shown in cases of multiple sclerosis (8). Focal lesions with reduced diffusivity are thought to be highly specific for ischemia, whereas new hyperintensities on T2-weighted MR images could arise from a number of alternative nonischemic pathologic abnormalities. Used in tandem with T2-weighted MR imaging, diffusion-weighted imaging may help to discriminate ischemic from nonischemic pathologic abnormalities and improve the overall value of serial MR imaging as a surrogate marker of disease. Correlation with a relevant clinical end point

is another important property of surrogate markers (23), and longitudinal studies are now required to determine whether the occurrence of new lesions is associated with cognitive decline or progressive disability.

A reduction of ADC values can be detected within minutes after acute stroke and usually persists for 7 to 10 days. Abnormalities shown on T2-weighted MR images develop more slowly, within the first few days after stroke, and generally persist. Hyperintensity on diffusion-weighted images is contributed to by a reduction in ADC values and by T2-weighted hyperintensity. Consequently, as ADC values fall, diffusion-weighted imaging findings become positive within minutes to hours after stroke. The findings are most hyperintense at 4 to 7 days but remain positive for a longer period because of the persistence of T2-weighted changes. The duration of diffusion-weighted imaging positivity is not known with certainty but is often quoted to be approximately 30 days.

Diffusion-weighted imaging hyperintensity due to T2-weighted changes beyond the period of ADC reduction is described as *T2 shine-through* (19). Assuming that ADC values are reduced within lesions for 10 to 14 days after the onset of ischemia, the estimated incidence of asymptomatic lesions, based on the frequencies in this study, is one lesion every 125 to 175 days for ischemic leukoaraiosis and one lesion every 95 to 133 days for CADASIL. This estimate is based on studies of acute stroke, in which the time course has been studied most extensively in large cohorts (24). However, less is known regarding the time course of diffusivity changes after lacunar stroke. One study has raised the possibility that the time course may be longer by observing that two lacunar lesions remained bright on diffusion-weighted images for 61 and 64 days, respectively (25). However, the reductions in ADC values reported for these two lesions were subtle, and T2 shine-through may have contributed to the persistent diffusion-weighted imaging hyperintensity. These findings are also in contrast to recent data that have suggested a similar time course of reduced ADC values after acute ischemia in all stroke subtypes, with reduced ADC values persisting at 1 week but not at 1 month after an event (20). The estimated incidences in the present study are also based on the assumptions that lesion frequency remains relatively constant with time in individual patients and that new lesions occur at approximately the same rate in all patients. An alternative possibility is that a subgroup of patients exists in whom new lesions occur fairly frequently. If this were true, it might be possible to perform clinical trials in smaller samples of patients selected by the presence of recent ischemic lesions shown on baseline images.

More accurate estimates of lesion frequency will require longitudinal studies, which will also help to resolve uncertainties regarding the evolution of diffusion abnormalities after lacunar stroke. The estimated frequencies from this study can be used to plan prospective studies and suggest that such studies are worthwhile. The frequency of false positive diffusion-

weighted imaging lesions (T2 shine-through) (Fig 1) in the present study highlights the importance of including a review of ADC maps to verify new lesions in the design of future studies.

Conclusion

This study showed that recent asymptomatic ischemic lesions can be detected in approximately 10% of patients with either ischemic leukoaraiosis or CADASIL. The potential role of asymptomatic infarction as a mechanism of progressive disability and cognitive decline needs to be examined in longitudinal studies. Detection of new lesions may be a useful surrogate marker of disease activity that could aid the development of much needed new therapies. The potential of this approach is worthy of further exploration in prospective studies.

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