PAPER

Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke

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Objective: To investigate whether the extent of white matter lesions (WML) on fluid attenuated inversion recovery (FLAIR) MRI sequences is an independent risk factor for recurrent stroke, and to document the pattern of acute cerebral infarcts using diffusion weighted imaging (DWI) in patients with different severities of WML.

Methods: In a prospective cohort study, 228 consecutive stroke patients were studied between 1999 and 2001 in a community hospital. The severity of WML was graded as 0 (no WML), 1 (mild), 2 (moderate), or 3 (severe) according to the FLAIR appearances. DWI was used to document the location and size of the infarct.

Results: 31 patients had grade 0 WML, 69 had grade 1, 59 had grade 2, and 69 had grade 3. Age was independently associated with WML on logistic regression analysis ($p = 0.0001$). Acute cerebral infarcts in deep white matter were correlated with increasing severity of WML. On a median follow up of 23.0 months, life table analysis showed that recurrent stroke was related to the severity of WML (recurrence rate 7.8% in grade 0, 9.3% in grade 1, 17.7% in grade 2, 43.7% in grade 3; $p = 0.0001$). Survival was reduced in patients with severe WML ($p = 0.0068$). A Cox proportional hazards model showed WML to be predictive of recurrent stroke ($p = 0.000$, hazard ratio = 4.177 (95% confidence interval, 2.038 to 8.564)) and also for survival ($p = 0.040$, hazard ratio = 2.021 (1.032 to 3.960)).

Conclusions: Patients with severe leukoaraiosis have increased risk of deep subcortical stroke and a higher risk of recurrent stroke.

Cerebral white matter lesions (WML) are often seen on computed tomography (CT) and magnetic resonance imaging (MRI) in patients admitted with a first stroke, and also in neurologically normal elderly individuals. The lesions are probably caused by cerebral ischaemia.[1] Arteriolosclerosis appears to be the most important causal factor in the development of such lesions, and the extent of WML is thought to reflect the extent of brain arteriolosclerosis. Pathological studies have consistently linked WML with demyelination, gliosis, necrosis, cavitation, and vacuolisation, conditions commonly associated with cerebrovascular disease.[2 3]

Diffusion weighted imaging (DWI) is an established imaging technique for visualising acute cerebral infarcts[4] and it has high sensitivity and specificity for subcortical stroke.[5] Previous small case series have shown that DWI is a useful tool for distinguishing acute from old ischaemic lesions in patients with severe leukoaraiosis.[6] However, there has been no large study on the pattern of acute infarcts in patients with different severities of WML.

There is considerable evidence from cross sectional and longitudinal studies for the association between WML and subsequent symptomatic stroke and cognitive impairment.[7–12] However, previous several studies exploring whether WML influence prognosis after a stroke have had conflicting results.[13–20] Moreover, there has been no large prospective study using fluid attenuated inversion recovery (FLAIR) sequences and DWI together. Our study was designed to determine the impact of WML on the prognosis of patients with first ever ischaemic stroke using these techniques.

METHODS

We recruited 338 consecutive patients with first ever acute ischaemic stroke who were admitted to the department of neurology of Huashan Hospital in Shanghai, China, between September 1999 and October 2001. Stroke was defined according to World Health Organisation criteria as rapidly developed clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin.[21] Patients with a previous history of either stroke (n = 43) or dementia (n = 11) before their index stroke were excluded. Assessment of prestroke dementia was based on a history of dementia according to the medical records. Patients younger than 40 years (n = 18) or with a history of severe head trauma or neurosurgery (n = 7) were also excluded. MRI was done within the first three weeks after the index stroke, and follow up was started three weeks after the index stroke. Early deaths (n = 11), patients with contraindications to MRI examination (n = 12), and those who refused it (n = 11) were excluded from the analysis. Thus in all 228 patients were included in the study.

Past medical history was recorded and routine biochemical blood tests were taken. In particular we recorded any history of hypertension (a systolic blood pressure of more than 160 mm Hg or a diastolic pressure of more than 90 mm Hg on repeated observations, or chronic antihypertensive treatment), duration of hypertension, presence of diabetes mellitus (chronic hypoglycaemic treatment before stroke), coronary heart disease (a history of angina pectoris or myocardial infarction), atrial fibrillation, smoking, and alcohol consumption.

Abbreviations: DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; WML, white matter lesion

Table 1 Clinical characteristics of patients with different severity of white matter lesions

Variable	Non-WML (n = 31)	Mild WML (n = 69)	Moderate WML (n = 59)	Severe WML (n = 69)	p Value
Male (n)	21 (67.7%)	38 (55.1%)	33 (55.9%)	38 (55.1%)	0.818
Age (y)	50.5 (5.2)	66.3 (6.7)	71.0 (5.9)	75.9 (7.1)	0.0001†
Hypertension (n)	13 (41.9%)	34 (49.3%)	41 (69.5%)	57 (82.6%)	0.0001*
Duration of hypertension (y)	2.7 (4.8)	5.4 (8.1)	10.3 (11.2)	13.7 (11.2)	0.0001†
SBP (mm Hg)	136.3 (26.9)	146.9 (32.3)	162.9 (33.8)	175.2 (30.7)	0.0001†
DBP (mm Hg)	83.1 (13.9)	87.0 (14.9)	92.3 (16.2)	97.3 (15.6)	0.001†
Diabetes mellitus (n)	3 (9.7%)	15 (21.7%)	17 (28.8%)	15 (21.7%)	0.226
Ischaemic heart disease (n)	1 (3.2%)	5 (7.2%)	10 (17.2%)	18 (26.1%)	0.004*
Atrial fibrillation (n)	3 (9.7%)	6 (8.7%)	6 (10.3%)	6 (8.7%)	0.987
Smoking (n)	10 (32.3%)	18 (26.1%)	13 (22.0%)	21 (30.4%)	0.659
Alcohol consumption (n)	6 (19.4%)	13 (18.8%)	11 (18.6%)	17 (24.6%)	0.805

Values are mean (SD) or n (%).
*χ^2 test, p value <0.05.
†One way analysis of variance.
DBP, diastolic blood pressure; SBP, systolic blood pressure; WML, white matter lesion; y, years.

MRI acquisition

All MRI examinations of the brain were done within three days of symptom onset with a 1.5 T scanner (GE Signa Horizon), using a head coil with quadrature detection. The brain imaging protocol involved the following:

- T1 and T2 weighted spin echo axial images (T1: time of repetition (TR)/time of echo (TE), 320/14 ms; T2: TR/TE, 2200/100 ms; matrix 256×160);
- sagittal T1 weighted images;
- FLAIR axial images (TR/TE, 8002/126 ms; inversion time (TI) = 2000 ms; matrix 256×160);
- axial isotropic diffusion weighted (DWI) SE echo planar imaging (EPI) sequence (TR/TE, 9999/101 ms; b = 0, 1000; matrix 128×128); all axial images had 5 mm slice thickness with 0.5 mm slice gap.

WML were considered present if visible as hyperintense lesions on the FLAIR MRI sequence, without prominent hypointensity on T1 weighted scans. They were rated on a 0 to 3 scale[22]: grade 0, no lesion (including symmetrical, well defined caps or bands); grade 1, focal lesions; grade 2, beginning confluence of lesions; grade 3, diffuse involvement of the entire region, with or without involvement of U fibres. DWI was used to evaluate the location and size of the new indexed cerebral infarcts. The location of new infarcts was classified into frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, deep white matter (including centrum semiovale and periventricular), cerebellum, brain stem, and multiple foci (infarcts that involved more than one of the above areas). The size of new cerebral infarcts was classified into lacunar infarcts (defined where the diameter of the lesion was no more than 15 mm on DWI) and non-lacunar infarcts. The MRIs were read without knowledge of the clinical data.

Group division and follow up

All patients were followed by regular clinic visits or by telephone calls. The end point events consisted of recurrent stroke or death. Stroke recurrence was defined as a new

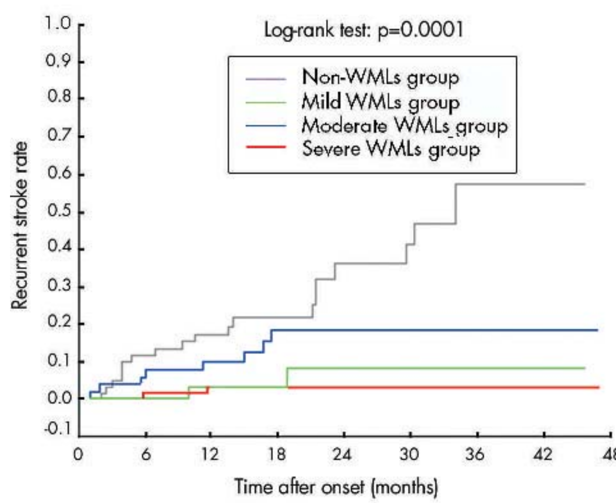

Figure 1 Kaplan–Meier recurrent stroke rate curves of patients with different grades of white matter lesion (WML).

Table 2 The location and size of new infarcts on diffusion weighted imaging of magnetic resonance images in the four groups

Infarct		Non-WML (n = 31)	Mild WML (n = 69)	Moderate WML (n = 59)	Severe WML (n = 69)	p Value
New infarcts on DWI	Frontal lobe	4 (12.9%)	4 (5.8%)	5 (8.5%)	3 (4.3%)	
	Parietal lobe	2 (6.5%)	2 (2.9%)	3 (5.1%)	3 (4.3%)	
	Temporal lobe	3 (9.7%)	1 (1.4%)	0 (0%)	2 (2.9%)	
	Occipital lobe	2 (6.5%)	1 (1.4%)	1 (1.7%)	3 (4.3%)	
Location	Basal ganglia	1 (3.2%)	9 (13.0%)	6 (10.2%)	7 (10.1%)	
	Deep WM	2 (6.5%)*	12 (17.4%)†	12 (20.3%)	29 (42.0%)	0.02
	Cerebellum	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)	
	Brain stem	1 (3.2%)	6 (8.7%)	5 (8.5%)	3 (4.3%)	
	Multi-foci	16 (51.6%)	34 (49.3%)	26 (44.1%)	19 (27.5%)	
Size	LI	3 (10.7%)	11 (15.9%)	10 (16.9%)	11 (15.9%)	
	Non-LI	28 (89.3%)	58 (84.1%)	49 (83.1%)	58 (84.1%)	0.82

*$p<0.05$, non-WML *v* severe WML.
†$p<0.05$, mild *v* severe WML.
LI, lacunar infarct; WM, white matter; WML, white matter lesion.

neurological deficit or an exacerbation of a previous deficit lasting more than 24 hours, according to Burn *et al*.[23] Cause of death was defined as the first stroke, recurrent stroke, and other reasons.

Statistical analyses

Statistical analysis software (SAS) 6.12 was used for the statistical analysis. A univariate analysis was carried out with *t* tests for continuous variables and the χ^2 test for categorical variables. The associations between the potential risk factors and the severity of WML were analysed by multiple logistic regression. The prognostic impact of WML on the risk of stroke recurrence and death was assessed with Kaplan–Meier event-free survival analyses (including a log-rank test to compare groups) and Cox proportional hazards regression modelling. A level of $p<0.05$ was considered statistically significant.

RESULTS

There were 31 patients with grade 0 WML, 69 with grade 1, 59 with grade 2, and 69 with grade 3 at the initial evaluation. In all, 145 patients had a history of hypertension before their index stroke among the 228 patients studied (13 with grade 0 WML, 34 with grade 1, 41 with grade 2, and 57 with grade 3). The clinical characteristics of the different groups are shown in table 1. There were significant differences among the four groups in terms of age, history of hypertension, duration of hypertension, absolute measurements of systolic and diastolic blood pressure, and ischaemic heart disease. Multiple logistic regression analysis showed that age was independently associated with WML ($p = 0.0001$).

Table 2 shows the location and size of the acute infarcts in the four groups. The extent of WML was strongly associated with the location of new lesions on DWI. Acute cerebral infarcts occurred more often in the deep white matter with increasing severity of WML.

Follow up data were obtained by clinic visits in 85 patients (37.3%), and by telephone interview in 132 patients (57.9%). The median follow up time was 23.0 months (range 0.9 to 37.1). During the follow up period, 11 cases (4.8%) dropped out, including one in grade 0 WML, five in grade 1, four in grade 2, and one in grade 3. At the end of the study, we had complete data on 217 patients for analysis.

Life table analysis shows the recurrent stroke rate in the four groups (fig 1). Recurrent stroke occurred in 29 patients (13.4%) including two in grade 0 WML (one with ischaemic stroke, the other with cerebral haemorrhage); three in grade 1 (one with ischaemic stroke, two with cerebral haemorrhage); eight in grade 2 (six with ischaemic stroke, two with cerebral haemorrhage), and 16 in grade 3 (15 with ischaemic stroke, one with cerebral haemorrhage). The one, two, and three year cumulative rates of recurrent stroke were 3.2%, 7.8%, and 7.8% in grade 0 WML; 3.2%, 3.2%, 9.3% in grade 1; 9.4%, 17.7%, 17.7% in grade 2; and 15.9%, 30.2%, 43.7% in grade 3. The recurrent stroke rate was significantly higher in patients with severe WML than in those with mild or no WML (log-rank test, $p = 0.0001$).

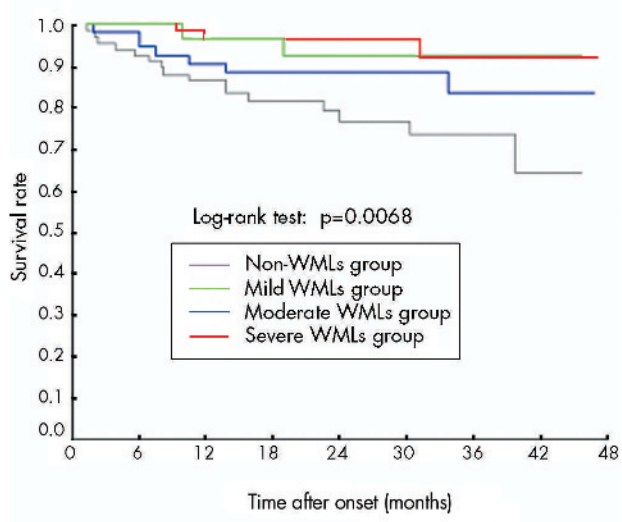

Figure 2 Kaplan–Meier survival rate curves of patients with different grades of white matter lesion (WML).

Assessment of the risk of recurrent stroke was repeated using Cox regression analysis. After the factors relating to the recurrent stroke listed in table 3 were taken into account, the extent of WML remained a significant predictor for recurrent stroke ($p = 0.000$; hazard ratio = 4.177 (95% confidence interval, 2.038 to 8.564)).

Figure 2 shows the survival rate curves of the four groups at the end of the study. Twenty five patients (11.5%) died during the follow up period: two in grade 0 (one from the first stroke, the other from a recurrent stroke); three in grade 1 (two from the first stroke, one from a recurrent stroke); six in grade 2 (four from the first stroke, one from a recurrent stroke, and one from other causes); and 14 in grade 3 (nine from the first stroke, three from a recurrent stroke, and two from other causes). The one year, two year, and three year cumulative rates of survival were 96.8%, 92.2%, and 92.2%, respectively, in grade 0 WML; 96.8%, 96.8%, and 92.0% in grade 1; 91.7%, 91.7%, and 83.7% in grade 2; and 87.5%,

Table 3 Cox model with the risk factors relating to recurrent stroke and survival rate

	Recurrent stroke			Survival rate		
Risk factor	p Value	HR	95% CI	p Value	HR	95% CI
Sex	0.475	1.498	0.495 to 4.538	0.916	0.947	0.345 to 2.603
Age	0.487	0.982	0.933 to 1.034	0.568	1.020	0.952 to 1.093
Hypertension	0.549	1.905	0.232 to 5.656	0.350	3.114	0.287 to 3.737
Systolic blood pressure	0.189	0.979	0.949 to 1.010	0.614	1.008	0.976 to 1.041
Diastolic blood pressure	0.329	1.022	0.978 to 1.068	0.469	1.016	0.973 to 1.060
Duration of hypertension	0.847	0.995	0.945 to 1.048	0.019*	0.938	0.889 to 0.989
Ischaemic heart disease	0.341	0.583	0.192 to 1.773	0.378	1.555	0.583 to 4.145
Diabetes mellitus	0.120	2.098	0.825 to 5.334	0.157	1.976	0.769 to 5.075
Atrial fibrillation	0.107	2.666	0.808 to 8.797	0.149	2.441	0.726 to 8.201
Smoking	0.196	2.188	0.668 to 7.160	0.250	2.023	0.609 to 6.726
Alcohol consumption	0.350	0.568	0.173 to 1.860	0.135	0.308	0.066 to 1.443
Severity of WML	0.000*	4.177	2.038 to 8.564	0.040*	2.021	1.032 to 3.960

*$p<0.05$.
CI, confidence interval; HR, hazard ratio; WML, white matter lesion.

78.8%, and 75.6% in grade 3. The survival rate was significantly lower in patients with severe WML than in those with no or mild WML (log-rank test, $p = 0.0068$).

Assessment of the survival rate was repeated using Cox regression analysis. After the factors relating to the survival rate listed in table 3 were taken into account, the extent of WML remained a significant predictor of survival ($p = 0.040$, hazard ratio = 2.021 (95% CI, 1.032 to 3.960)). Other predictors of survival are shown in table 3.

DISCUSSION

The two major findings of this prospective study of stroke patients were that acute deep white matter infarcts, as shown on DWI, and further strokes are both related to the severity of WML. DWI can distinguish acute infarct from old ischaemia[5 6 24] and is thus ideal for showing the exact location of acute infarcts in patients with severe WML, which CT cannot do. Our data showed that the more severe the WML, the more likely it is that an acute infarct is located in the deep white matter. This result support the hypothesis that severe WML may in part be a sequel of multiple acute infarcts of the deep white matter.

The strength of our study includes the use of advanced magnetic resonance imaging such as FLAIR and DWI. FLAIR is reported to be more sensitive for detecting periventricular lesions than T2 sequences, and can effectively differentiate small ischaemic lesions from dilated perivascular spaces in the deep white matter.[25–27] To the best of our knowledge, this study is the first to determine the impact of WML on the prognosis of patients with first ever ischaemic stroke using functional MRI techniques.

We also found that the extent of WML in the index stroke was a strong predictor of recurrent stroke and of increased mortality. The three year cumulative incidence of recurrent stroke (43.7%) in the patients with severe WML was more than four times as great as in the patients with mild WML (9.3%) or with no WML (7.8%). Life table analysis showed the survival rate in the severe WML group was lower than in the mild WML or no WML groups.

The results of our study are in agreement with previous reports that assessed WML on CT but not on MRI. In the Dutch TIA trial, the risk of stroke was 15% in 337 patients with WML, compared with 8.0% in 2680 patients without WML.[14] In the north American symptomatic carotid endarterectomy trial (NASCET), the three year risk of stroke for medically treated patients was 37.2% in 69 patients with widespread WML, compared with 27.3% in 173 patients with limited WML and 20.2% in 1073 patients with no WML.[17] An American study of 221 patients with ischaemic stroke indicated that severe WML predicted increased morbidity and mortality over patients with mild or no WML.[18] In a Japanese study of 215 patients with lacunar infarcts, the 95 patients with WML had a significantly increased risk of recurrent stroke or death.[13]

Our study has certain weaknesses that needed to be acknowledged. First, this was a hospital based study which may not be representative of stroke patients in the community. However, it is difficult to use sophisticated neuroimaging technique such as functional MRI in the community setting. Second, cognitive function was not assessed in our cohort. Recent studies have indicated that WML may be associated with cognitive impairment,[28] although this has not been fully established. The inclusion of cognition assessment will further clarify the clinical significance of WML. Finally, we did not include stroke severity in our study. Stroke severity is likely to be important in predicting death and recurrent events.

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REFERENCES

1 **Pantoni L**, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke* 1997;**28**:652–9.
2 **Munoz DG**, Hastak SM, Harper B, *et al.* Pathologic correlates of increased signals of the centrum ovale on magnetic resonance imaging. *Arch Neurol* 1993;**50**:492–7.
3 **van Swieten JC**, van den Hout JH, van Ketel BA, *et al.* Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. *Brain* 1991;**114**:761–74.
4 **Fisher M**, Prichard JW, Warach S. New magnetic resonance techniques for acute ischemic stroke. *JAMA* 1995;**274**:908–11.
5 **Singer MB**, Chong J, Lu D, *et al.* Diffusion-weighted MRI in acute subcortical infarction. *Stroke* 1998;**29**:133–6.
6 **Okada K**, Wu LH, Kobayashi S. Diffusion-weighted MRI in severe leukoaraiosis. *Stroke* 1999;**30**:478–9.
7 **Garde E**, Mortensen EL, Krabbe K, *et al.* Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. *Lancet* 2000;**356**:628–34.
8 **de Groot JC**, de Leeuw FE, Oudkerk M, *et al.* Cerebral white matter lesions and cognitive function: the Rotterdam scan study. *Ann Neurol* 2000;**47**:145–51.
9 **De Groot JC**, De Leeuw FE, Oudkerk M, *et al.* Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol* 2002;**52**:335–41.
10 **Vermeer SE**, Hollander M, van Dijk EJ, *et al.* Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003;**34**:1126–9.
11 **Wong TY**, Klein R, Sharrett AR, *et al.* Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA* 2002;**288**:67–74.
12 **Yamauchi H**, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. *J Neurol Neurosurg Psychiatry* 2002;**72**:576–82.
13 **Miyao S**, Takano A, Teramoto J, *et al.* Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke* 1992;**23**:1434–8.
14 **van Swieten JC**, Kappelle LJ, Algra A, *et al.* Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. *Ann Neurol* 1992;**32**:177–83.
15 **van Zagten M**, Boiten J, Kessels F, *et al.* Significant progression of white matter lesions and small deep (lacunar) infarcts in patients with stroke. *Arch Neurol* 1996;**53**:650–5.
16 **Inzitari D**, Cadelo M, Marranci ML, *et al.* Vascular deaths in elderly neurological patients with leukoaraiosis. *J Neurol Neurosurg Psychiatry* 1997;**62**:177–81.
17 **Streifler JY**, Eliasziw M, Benavente OR, *et al.* Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke* 2002;**33**:1651–5.
18 **Briley DP**, Haroon S, Sergent SM, *et al.* Does leukoaraiosis predict morbidity and mortality? *Neurology* 2000;**54**:90–4.
19 **Jorgensen HS**, Nakayama H, Raaschou HO, *et al.* Leukoaraiosis in stroke patients. The Copenhagen Stroke Study. *Stroke* 1995;**26**:588–92.
20 **Wiszniewska M**, Devuyst G, Bogousslavsky J, *et al.* What is the significance of leukoaraiosis in patients with acute ischemic stroke? *Arch Neurol* 2000;**57**:967–73.
21 **Anonymous**. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;**20**:1407–31.
22 **Wahlund LO**, Barkhof F, Fazekas F, *et al.* A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001;**32**:1318–22.
23 **Burn J**, Dennis M, Bamford J, *et al.* Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 1994;**25**:333–7.
24 **Helenius J**, Soinne L, Salonen O, *et al.* Leukoaraiosis, ischemic stroke, and normal white matter on diffusion-weighted MRI. *Stroke* 2002;**33**:45–50.
25 **Herskovits EH**, Itoh R, Melhem ER. Accuracy for detection of simulated lesions: comparison of fluid-attenuated inversion-recovery, proton density—weighted, and T2-weighted synthetic brain MR imaging. *Am J Roentgenol* 2001;**176**:1313–18.
26 **Ikeda Y**, Matsumoto K, Hayashi T, *et al.* [Use of fluid-attenuated inversion recovery (FLAIR) images in brain check-up.] *No To Shinkei* 1999;**51**:933–7.
27 **Ohta K**, Obara K, Yogo Y, *et al.* [Chronological changes of lacunar infarctions on fluid-attenuated inversion recovery magnetic resonance images.] *Rinsho Shinkeigaku*, 2001;**41**:277–82.
28 **Geroldi C**, Galluzzi S, Testa C, *et al.* Validation study of a CT-based weighted rating scale for subcortical ischemic vascular disease in patients with mild cognitive deterioration. *Eur Neurol* 2003;**49**:193–209.