RESEARCH PAPER

Neuroimaging predictors of death and dementia in a cohort of older stroke survivors

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ABSTRACT

Background Stroke is a risk factor for subsequent death and dementia. Being able to identify subjects at particular risk would be beneficial to inform treatment and patient management.

Methods Subjects aged over 75 years with incident stroke were recruited. Subjects had a cognitive assessment at 3 months post stroke to exclude dementia, and had an MRI scan (n=106) at that time. Subjects were then followed longitudinally for incident dementia and/or death.

Results Independent neuroimaging predictors of survival to dementia were medial temporal atrophy (MTA; p=0.013) and the presence of thalamic infarcts (p=0.002). After inclusion of cognitive score in the model, the significance of MTA (p=0.049) and thalamic infarcts (p=0.04) was reduced, with survival being best predicted by baseline cognitive score (p=0.004). The only independent significant predictor of survival to death was MTA. Apart from thalamic infarcts, the NINDS/AIREN neuroimaging criteria did not independently predict survival to death or dementia.

Conclusions MTA was associated with shorter time to dementia, suggesting a role for Alzheimer pathology in the development of post stroke dementia.

INTRODUCTION

In people with stroke, dementia is common, and may be a direct consequence of the stroke in 15%, and be pre-existing in a further 10% of subjects.[1] However, stroke is also a risk factor for dementia in the long term.[1][2]

Risk factors which have been identified for development of dementia after stroke include medial temporal atrophy (MTA) and white matter hyperintensities (WMH), as seen on T2 weighted MRI imaging.[1]

The criteria of the National Institute of Neurological Disorders and Stroke Association/Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS/AIREN) are widely used to diagnose vascular dementia (VaD).[3] Evidence of cerebrovascular disease is required, and the report includes specific criteria for the identification of vascular lesions on neuroimaging. We have previously found in a group of patients, including those studied in this report, that the criteria did not differentiate between post stroke subjects with and without dementia,[4] and in this study we examined whether they were predictive of dementia incidence in the initially non-demented cohort.

Severity of WMH on neuroimaging is a significant predictor of long term survival after stroke.[5] Few studies have examined the role of MTA in long term survival post stroke, although in the general population both MTA and WMH predict lower survival time in those attending memory clinics.[6−8]

In this cohort of initially non-demented older stroke survivors, we have previously demonstrated associations between both WMH and MTA and cognition within a few years of stroke.[9][10] Here we look at the predictive ability of MTA, WMH and the NINDS/AIREN neuroimaging criteria on survival time over an 8 year period to dementia, and to death. Based on our earlier findings and previous literature, we hypothesised that MTA and WMH would be significant predictors of death and dementia, whereas the NINDS/AIREN criteria would not.[4]

METHODS

Subjects

Stroke patients taking part in this imaging investigation were a previously described cohort[11] which has been followed longitudinally. Older stroke patients (n=706) ≥75 years were pre-screened consecutively between 2000 and 2002 from representative hospital based stroke registers in Tyneside, Wearside and Teesside (UK) from seven hospitals. Patients were over 75 years of age at the time of the stroke, defined using the WHO criteria. Patients were comprehensively assessed at 3 months post stroke using a standardised battery comprised of medical history, Mini-Mental State Examination (MMSE) score, assessment of neurological deficits, blood screen and review of CT brain scan undertaken at the time of stroke, and were excluded if they: (i) had significant physical illness and disabilities that precluded neuropsychological evaluation (eg, visual impairment, aphasia, hemiparesis affecting the hand used for writing); (ii) had a diagnosis of dementia according to DSM-IIIR criteria; or (iii) declined to take part. Following general practitioner approval and discussion of the study, 355 of the original 706 subjects were eligible for the post stroke survivor study. DSM-IIIR criteria were used because they include a general definition for dementia, unlike DSM-IV, which presumes aetiology, and we were interested in post stroke dementia regardless of cause. The total number of MRI scans was limited by cost to approximately 100, so not all subjects were approached. Instead, eligible subjects were consecutively invited to have an MRI scan until 108 had

agreed. The analysis here is a subset of a separate paper looking at survival in the whole cohort with regard to cardiovascular risk factors.[12] Subjects underwent an annual clinical and cognitive assessment. The appropriate local research ethics committee granted ethics approval for the study. Following full explanation and discussion of the study, patients gave their consent to the evaluations, with additional assent from the next of kin.

Neuropsychological testing

To evaluate global cognitive performance, we used the Cambridge Cognitive Assessment-revised, section B (CAMCOG-R),[13] which is a standardised paper and pencil test for global cognition (maximum score, 105). It has subscores for several cognitive domains, including executive function, and includes the MMSE.

Diagnosis of dementia

On annual review, further evaluation for possible dementia using DSM-IIIR dementia criteria was performed if a participant was unable to complete an MMSE, or scored less than 24 on the MMSE, or scored 2 or more points less on the MMSE than 12 months previously, or if any other signs of cognitive impairment were apparent during their annual neuropsychological evaluation. Criteria for dementia were applied by an experienced dementia specialist, blind to results from MR imaging changes.

MRI acquisition

All patients were imaged using a 1.5 T GE Signa scanner (General Electric, Milwaukee, USA). Coronally oriented whole brain T1 weighted three-dimensional FSPGR data sets were acquired (repetition time=12.4 ms, echo time=4.2 ms, inversion time=650 ms, pixel size 0.78×0.78, 1.6 mm slice thickness, flip angle=15°) along with axial whole brain FLAIR images (TR=10000 ms, TE=125 ms, TI=2100 ms, slice thickness=5 mm, interslice gap=0.3 mm). Images were obtained at baseline.

Volume of white matter hyperintensities

Volume of WMH was obtained from the baseline MRI images using previously validated automated software[14] Briefly, spm99 (http://www.fil.ion.ucl.ac.uk/spm) was used to segment the brain from the FLAIR images. Volumes of WMH were then determined by applying an intensity threshold of 1.45 times the modal intensity for each slice to segment the WMH. The accuracy of this was checked visually for each subject and the total WMH volume in the whole brain was calculated. Values in table 1 are WMH (in ml) for ease of interpretation, however for the statistical analysis, we calculated the ratio of WMH volume to total brain volume, and in order to produce normally distributed data used a log transform.

MRI rating

Extent of medial temporal lobe atrophy (right and left) was rated using a standardised scale[15] from hard copies of the baseline T1 weighted coronal images. This scale rates atrophy (0, absent; 1, minimal; 2, mild; 3, moderate; and 4, severe) based on the width of the surrounding CSF spaces (temporal horn and choroid fissure) and the height of the hippocampal formation (which includes the hippocampus proper, subiculum, and para-hippocampal and dentate gyri). Left and right scores were summed to give an overall combined MTA score (maximum score 8). All scans were rated by consensus between three trained and experienced raters (RB. JTO and EJB).

At the same time, the criteria for vascular lesions, as specified by NINDS/AIREN, were also documented for each patient.

Table 1 Subject characteristics (n=106)

Age at baseline (years)	79.8 (4.11)
Sex (F:M)	57:49
Deceased during follow-up (n (%))	60 (57)
Developed dementia during follow-up (n (%))	27 (25)
CAMCOG-R score	84.4 (8.53)
MMSE score	26.2 (2.69)
GDS score	3.37 (2.96)
WMH (ml)	2.08 (1.81)
MTA	2.71 (1.75)
Total brain volume (ml)	1009 (82.4)
Oxford Stroke Classification (LACS/PACS/TACS/POCS/unknown)	35/42/5/17/7
Any previous stroke/TIA (n=103) (n (%))	30 (29)
Previous stroke (residual disability) (n=103) (n (%))	15 (15)
Hypertension (n=105) (n (%))	64 (61)
Atrial fibrillation (n=105) (n (%))	17 (16)
Diabetes mellitus (n=101) (n (%))	5 (5)
Current smoker (n (%))	18 (17)
Ischaemic heart disease (n=105) (n (%))	36 (34)
Cortical lesion 40 mm or larger (n (%))	25 (24)
AIREN bilateral anterior cerebral artery large infarct (n (%))	0 (0)
AIREN bilateral large vessel infarct (n (%))	3 (3)
AIREN large vessel—left infarct (n (%))	15 (14)
AIREN large vessel—right infarct (n (%))	25 (24)
AIREN association areas large infarct (n (%))	27 (26)
AIREN posterior cerebral artery stroke (n (%))	11 (10)
AIREN bilateral thalamic infarct (n (%))	6 (6)
AIREN basal ganglia small vessel disease (n (%))	65 (61)
AIREN periventricular WMH (n (%))	43 (41)
AIREN frontal WMH (n (%))	47 (44)
AIREN WMH >25% (n (%))	27 (26)
AIREN any (n (%))	102 (96)
Any thalamic infarct (n (%))	40 (38)

Values are mean (SD) or n (%).
AIREN, relevant imaging change meets imaging criteria as specified in the National Institute of Neurological Disorders and Stroke Association/Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS/AIREN) criteria; CAMCOG-R, Cambridge Cognitive Assessment-revised; GDS, Geriatric Depression 15 point Scale; LACS/PACS/TACS/POCS, lacunar/partial anterior/total anterior/posterior syndrome; MTA, medial temporal lobe atrophy rating; MMSE, Mini-Mental State Examination; TIA, transient ischaemic attack; WMH, white matter hyperintensity volume.

These are broadly classed under: (a) multiple large infarcts, (b) strategic single infarcts (eg, angular gyrus) or thalamus or (c) small vessel disease with extensive leukoaraiosis, or multiple basal ganglia lacunes. Operational criteria for classifying such lesions were suggested by van Straaten and colleagues.[16] WMHs were rated from hard copies of FLAIR images acquired in the axial plane. As part of the NINDS/AIREN criteria, those with extensive periventricular WMHs and leukoencephalopathy involving at least 25% of the total white matter were recorded. All scan measurements and ratings were undertaken over the baseline period, blind to clinical findings and before follow-up data had been collected.

Statistical analysis

Statistical analysis was performed with SPSS (V.17.0). In order to examine the associations between exposure to putative risk factors for death or dementia, Cox proportional regression analyses were used to obtain univariate proportional HRs for each risk factor, using time (days) from index stroke to death and dementia as the dependent variables. In the dementia model, if a patient died, data were right censored. The date of onset of dementia was assumed to be at the midpoint between the two assessments where dementia status changed. HRs were

given according to presence or absence of the risk factor, or per point on quantitative scales, as appropriate. There were no missing data in the variables we examined.

Following identification in univariate models, significant predictors of death and dementia were entered into a multivariate Cox regression model. Where similar features were described by more than one significant predictor, the predictor with the higher level of significance in univariate analyses was entered into multivariate analyses, in order to avoid coaggregation of predictors (eg, WMH volume rather than AIREN WMH >25%). Multivariate Cox models were examined to see if the proportional hazard assumption was met (using the R program V2.10, http://cran.r-project.org/) by investigating the scaled Schoenfeld residuals graphically and correlating the residuals against time. Non-linearity was investigated using graphical inspection of Martingale residuals plotted against covariates.

RESULTS

Of the 108 subjects who underwent MRI, two moved during the scan, leaving 106 successful scans for analysis. Table 1 shows the demographics of the study group. Subjects were followed-up for a median of 3.18 (IQR 4.78) years to last dementia assessment, and a median of 6.62 (IQ range 4.05) years for deaths. All subjects (apart from two) were followed-up until either death or 9 years after initiation of the study. Of those whose final status was 'without dementia' (n=79), there were 55 (71%) who had an assessment of dementia within 1 year of their last recorded vital status. There were no significant differences between those with successful MRI (n=106) versus those who did not have an MRI scan (n=249) in age (79.8 (SD 4.1) vs 80.3 (SD 4.1); t=1.2, p=0.25), CAMCOG-R score (84.4 (SD 8.5) vs 85.3 (SD 9.1); t=0.914, p=0.36), sex (F/M=57/49 vs 135/114; χ^2=1.90, p=0.17) or Oxford Community Stroke Classification (lacunar/ partial anterior/total anterior/posterior syndrome/unknown

35/42/5/17/7 (33/40/5/16/7%) vs 81/103/14/32/19 (33/41/6/ 13/8%; χ^2=0.829, p=0.94).

Table 2 presents results of univariate Cox survival analysis for time to dementia. Significant neuroimaging predictors of shorter time to dementia onset were MTA and volume of WMH, along with age, sex and both CAMCOG-R and MMSE scores at baseline. Both MTA (ρ=−0.271; p=0.005) and WMH (ρ=−0.253; p=0.009) were significantly correlated with baseline CAMCOG-R score. Of the NINDS/AIREN neuroimaging criteria, the presence of bilateral thalamic infarcts along with WMH predicted survival. In a Cox multivariate model with age, and the significant neuroimaging variables, independent predictors of survival time to dementia were MTA (p=0.031, HR=1.34 (95% CI 1.03 to 1.75)), WMH volume (p=0.037, HR=1.90 (1.04 to 3.48)) and the presence of thalamic lesions (p=0.004, 5.20 (1.7 to 15.9)). Examining the model, there was no non-linearity in the continuous variables, however, there was evidence of a non-proportional hazard for age. We therefore repeated the analysis, stratifying for age (in groups of 75−79 years (n=59), 80−84 years (n=32) and age >85 years (n=15)). Results of this are shown in table 3 (model fit χ^2=24.0, p<0.001).

With the addition of CAMCOG-R score to the model (table 3, model fit χ^2=34.4, p<0.001), the significant predictors were CAMCOG-R (p=0.004), thalamic lesions (p=0.040) and MTA (p=0.049). Figure 1A shows a univariate survival curve of CAMCOG-R versus time to dementia. Using MMSE rather than CAMCOG-R produced almost identical results, with MMSE strongly predicting survival in the multivariate analysis (p=0.004).

Table 4 has the results of the Cox univariate survival analysis for time to death. Significant predictors were age, MTA and CAMCOG-R score. None of the NINDS/AIREN neuroimaging variables was significantly associated with survival time to death (data not shown). In a multivariate model with age and MTA (table 5), survival time was predicted by MTA (χ^2 for model fit 10.3, p=0.006). There was no evidence of non-linearity or non-proportional hazards in the model. Adding CAMCOG-R score did not significantly improve the model (change in model χ^2 1.8, p=0.2). Figure 1B shows a survival curve of MTA versus survival to death.

DISCUSSION

Our principal finding was that in this older cohort of non-demented stroke survivors, the presence of MTA at baseline was

Table 2 Univariate Cox survival model for time to dementia

	p Value	HR (95% CI)
Age (years)	0.003	1.12 (1.04 to 1.21)**
Male sex	0.806	0.909 (0.425 to 1.95)
MTA	0.003	1.43 (1.13 to 1.80)**
Log (WMH/TBV)	0.001	2.42 (1.41 to 4.16)**
Total brain volume (ml)	0.183	0.995 (0.989 to 1.00)
Cortical lesion 40 mm or larger	0.551	0.724 (0.250 to 2.10)
AIREN association areas	0.695	1.19 (0.502 to 2.81)
AIREN post-cerebral artery infarct	0.707	0.759 (0.179 to 3.21)
AIREN basal ganglia	0.938	1.03 (0.472 to 2.25)
AIREN frontal WMH	0.680	1.17 (0.550 to 2.50)
AIREN periventricular WMH	0.013	2.65 (1.23 to 5.74)*
AIREN bilateral thalamic infarct	<0.001	6.47 (2.42 to 17.3)**
AIREN large vessel—left	0.874	1.09 (0.376 to 3.16)
AIREN large vessel—right	0.457	0.668 (0.231 to 1.93)
AIREN bilateral large vessel	0.524	0.047 (0.000 to 580)
AIREN WMH >25%	0.025	2.41 (1.11 to 5.19)*
AIREN sum of scores	0.024	1.40 (1.05 to 1.87)*
Any thalamic infarct	0.436	1.35 (0.633 to 2.89)
CAMCOG-R	<0.001	0.902 (0.865 to 0.941)**
MMSE	<0.001	0.716 (0.620 to 0.826)**

*p<0.05; **p<0.01.
AIREN, relevant imaging change meets imaging criteria as specified in the National Institute of Neurological Disorders and Stroke Association/Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS/AIREN) criteria; CAMCOG-R, Cambridge Cognitive Assessment-revised; MMSE, Mini-Mental State Examination; MTA, medial temporal lobe atrophy rating; TBV, total brain volume; WMH, white matter hyperintensity volume.

Table 3 Multivariate Cox model of survival to dementia with significant neuroimaging predictors stratified by age, and with addition of cognitive score

	p Value	HR (95% CI)
Significant neuroimaging predictor		
MTA	0.013	1.42 (1.08 to 1.86)
Log (WMH/TBV)	0.060	1.81 (0.976 to 3.34)
AIREN bilateral thalamic lesions	0.002	8.49 (2.17 to 33.2)
Significant neuroimaging + cognitive score predictors		
MTA	0.049	1.32 (1.00 to 1.75)
Log (WMH/TBV)	0.146	1.59 (0.851 to 2.96)
AIREN bilateral thalamic lesions	0.040	4.11 (1.07 to 15.8)
CAMCOG-R	0.004	0.929 (0.884 to 0.976)

AIREN, relevant imaging change meets imaging criteria as specified in the National Institute of Neurological Disorders and Stroke Association/Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS/AIREN) criteria; CAMCOG-R, Cambridge Cognitive Assessment-revised; MTA, medial temporal lobe atrophy rating; TBV, total brain volume; WMH, white matter hyperintensity volume.
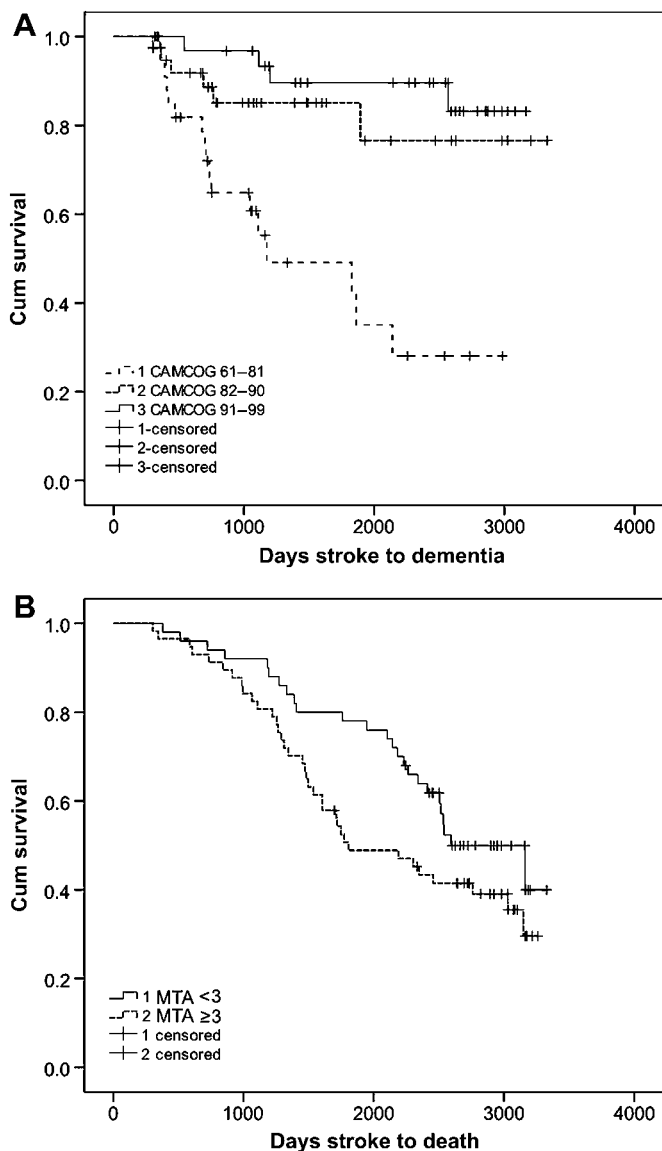
Table 4 Univariate Cox model of survival to death

	p Value	HR
Age (years)	0.012	1.08 (1.02 to 1.15)*
Male sex	0.40	1.25 (0.751 to 2.08)
MTA	0.009	1.23 (1.06 to 1.44)**
Log (WMH/TBV)	0.288	1.18 (0.870 to 1.60)
Total brain volume (ml)	0.142	0.997 (0.993 to 1.00)
CAMCOG-R	0.020	0.967 (0.939 to 0.995)*
MMSE	0.053	0.915 (0.836 to 1.00)

*p<0.05; **p<0.01.
CAMCOG-R, Cambridge Cognitive Assessment-revised; MTA, medial temporal lobe atrophy rating; MMSE, Mini-Mental State Examination; TBV, total brain volume; WMH, white matter hyperintensity volume.

Figure 1 Univariate survival. (A) Time to dementia by Cambridge Cognitive Assessment-revised (CAMCOG-R) score in three groups—CAMCOG-R >90 (n=31), CAMCOG-R 82—90 (n=38) and CAMCOG-R <82 (n=37). (B) Time to death by medial temporal atrophy (MTA) in two groups—MTA <3 (n=50) and MTA ≥3 (n=56).

vessel than large vessel stroke, in agreement with the findings of Staekenborg[17] who reported that the majority of VaD cases had small vessel disease. This is also consistent with the finding that the prevalence of post stroke dementia, albeit in younger subjects, was associated with lacunar infarcts in a 24 year population based study.[18]

We also found a relationship between bilateral thalamic lesions and dementia, which supports previous work suggesting such a link.[19–21] The presence of any thalamic infarct was not a significant predictor of cognitive decline (table 2), suggesting that more extensive thalamic involvement is required before cognition is affected. However, our finding must be treated with caution as only six subjects had bilateral thalamic lesions.

The best predictor of survival time to post stroke dementia was cognitive score 3 months post stroke. Other studies have also found this to be the case in younger subjects.[22] In the larger cohort from which this imaging study was drawn, cognitive score, along with cardiovascular risk factors, predicted survival time to dementia.[12] This suggests that poor cognitive status shortly after stroke is indicative of ongoing cognitive decline, or that there is a threshold of cognitive damage which it is difficult to recover from. As this was an incident study, we do not have information about the cognitive status of participants before the stroke, and it is possible that some mild cognitive impairment preceded the stroke, although we did rule out dementia immediately post stroke.[23 24]

We found that MTA was the best predictor of survival time to death whereas WMH did not predict survival time. This is contrary to a previous study which reported an association with WMH,[5] however, differences between the studies are that our subjects were on average 10 years older. The mechanism for this association of MTA with survival is unclear although the hippocampus is relatively sensitive to hypoperfusion so MTA

associated with shorter survival time to subsequent onset of dementia, suggesting a role for Alzheimer's type pathology as a cause of post stroke dementia. However, baseline CAMCOG-R score was a much stronger predictor of survival to dementia. We did not see any association between dementia and large vessel stroke although the numbers with AIREN large vessel infarcts were relatively small so the study may have been underpowered to detect such an association. Our findings are in keeping with previous studies in generally younger stroke patients[1] showing the influence of MTA and WMH on post stroke dementia. We examined the role of the NINDS/AIREN neuroimaging criteria for VaD and, apart from thalamic lesions and WMHs, did not find any increased rate of dementia in those meeting the individual criteria. This is in keeping with our previous study in which we found that there was no difference between the NINDS/AIREN neuroimaging criteria in those with acute post stroke dementia versus those without.[4] The results suggest that post stroke dementia is associated more strongly with small

Table 5 Multivariate Cox model of survival to death with age and significant neuroimaging predictors and with CAMCOG-R score also added

	p Value	HR
Age + significant neuroimaging predictors		
Age (years)	0.072	1.06 (0.995 to 1.13)
MTA	0.039	1.19 (1.01 to 1.40)
Age + significant neuroimaging + CAMCOG-R score predictors		
Age (years)	0.156	1.05 (0.983 to 1.12)
MTA	0.075	1.17 (0.985 to 1.38)
CAMCOG-R	0.163	0.978 (0.949 to 1.01

CAMCOG-R, Cambridge Cognitive Assessment-revised; MTA, medial temporal lobe atrophy rating.

may be a proxy measure of the general level of hypoperfusion. Untreated hypertension has been shown to be associated with MTA[25] and perhaps the presence of poorly controlled vascular risk factors contributed to survival. Although we did not find total brain volume to predict survival, it is possible that atrophy in strategic locations in the brain might contribute. Future research should look at associations between survival and regional atrophy throughout the brain using techniques such as voxel based morphometry.

Although our subsample of 106 subjects with MRI was representative of the 355 in the main cohort, there is the possibility of selection bias—those who declined participation may have had more severe stroke (or specific types of stroke), and although we have details on survival to death on practically all subjects, the follow-up to dementia was less complete due to difficulty in arranging a cognitive assessment or the patients died before dementia was noted. We assessed people 3 months after stroke in order to minimise the acute effects of stroke on cognitive assessment but this may have resulted in selection bias against those who died in the 3 months. We had relatively small numbers of patients with large vessel stroke, and there may be a selection bias here, with those included being unrepresentative of large vessel stroke patients in general.

WMH had no significant association with dementia when the model was stratified according to age. It is possible that age related changes to the T1 value of the brain meant that the brightness of WMH (and hence the automatically segmented volume of WMH) varied with age.

A limitation of the study is that we did not have information regarding cognitive status before stroke, as it is likely that the stroke will have caused some decline in cognitive function, even though we excluded subjects with dementia. It is probable that cognitive ability before stroke would be associated with longer survival to dementia due to mechanisms associated with cognitive reserve.

Recent research has suggested that microbleeds (areas of hypointensity on T2* weighted MR images) may be predictive of mortality and cognitive decline.[6 26] Microbleeds are common in both stroke and Alzheimer's disease. A limitation of this study is that we could not analyse microbleeds with the imaging sequences we acquired. Future research should investigate to what extent microbleeds additionally contribute to survival. Strengths of the study include a well characterised group of older post stroke survivors who did not have dementia immediately after stroke and who were followed-up for an extensive period of time.

In summary, we found that MTA and WMH were associated with incidence of dementia but that cognitive status 3 months post stroke was the best predictor of survival time to dementia. If confirmed in other studies, this would be a useful clinical indicator of likely decline in older stroke survivors.

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