Through the looking glass: Risk factors, radiological hallmarks and cognitive function in cerebral small vessel disease

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Risk factor profiles of patients with new lacunar infarcts in deep white matter and basal ganglia. The SMART-MR study

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ABSTRACT

Background There is evidence that lacunar infarcts can have different aetiologies, possibly related to their anatomical location and vascular territory. We investigated the risk factor profiles of patients with new lacunar infarcts in the basal ganglia and deep white matter.

Methods Within the SMART-MR study, a prospective cohort on brain changes on MRI in patients with symptomatic atherosclerotic disease, 679 patients (57±9 years) had vascular screening and MRI at baseline and after a mean follow-up of 3.9 years. We investigated the relation between vascular risk factors at baseline and appearance of new lacunar infarcts in the basal ganglia and deep white matter at follow-up.

Results New lacunar infarcts appeared in 44 patients in the basal ganglia and in 37 patients in the deep white matter. In multivariable analysis, older age, history of cerebrovascular disease and baseline WMH volume were associated with increased risk of new lacunar infarcts in both anatomical locations. Hyperhomocysteinemia was associated with increased risk of lacunar infarcts in the basal ganglia (RR=2.0, 95% CI 1.0 to 4.2), whereas carotid stenosis >70% (RR=2.5, 1.2 to 5.0), smoking (per packyear; RR=1.01, 1.01 to 1.03), hypertension (RR=3.4, 1.2 to 9.7) and progression of WMH volume (RR=2.4, 1.1 to 5.2) were associated with increased risk of lacunar infarcts in the deep white matter.

Conclusion Risk factor profiles for new lacunar infarcts in basal ganglia and deep white matter are different, suggesting different aetiologies. The independent association between progression of WMH and new deep white matter lacunar infarcts suggest a common aetiology for these radiological abnormalities.
INTRODUCTION

Lacunar infarcts of presumed vascular origin, together with white matter hyperintensities of presumed vascular origin (WMH), are one of the hallmarks of cerebral small vessel disease (CSVD). They are ischemic lesions, identified on MRI, which can be silent or can lead to clinical symptoms. It is suggested that anatomical location of lacunar infarcts is important with respect to their aetiology and clinical consequences. Lacunar infarcts in the deep white matter are often clinically silent and often appear in or nearby confluent white matter lesions. It has been hypothesized that these lacunar infarcts appear gradually under the influence of chronic ischemia due to arteriolosclerosis or endothelial damage with breakdown of the blood brain barrier. In contrast, lacunar infarcts in the basal ganglia often lead to clinical symptoms, such as a pure motor or sensory stroke, because of their strategic location and often larger size. It has been found that these lesions appear more acutely and are more strongly related to large cortical infarcts, and therefore it is thought that (thrombo-embolic) occlusion of the perforating arteries is the underlying pathophysiological mechanism. Risk factors seem to differ as well. Risk factors associated with chronic hypoperfusion and small vessel disease, such as carotid stenosis and hypertension have been associated with lacunar infarcts in the deep white matter, whereas risk factors more commonly associated with large vessel disease, such as atrial fibrillation are associated with lacunar infarcts in the basal ganglia. Only few studies reported on risk factors for both lacunar infarcts in deep white matter and basal ganglia in the same population, and only one was a longitudinal study on new lacunar infarcts. We examined the longitudinal association between baseline vascular risk factors and new lacunar infarcts in the deep white matter and basal ganglia. We hypothesized that patients with lacunar infarcts in deep white matter and basal ganglia have different risk factor profiles.

PATIENTS AND METHODS

Subjects

We used data from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study to investigate brain changes on MRI in 1309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere. Between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or...
an abdominal aortic aneurysm (AAA), and without MR contraindications, were invited to participate. Coronary artery disease was defined as myocardial infarction, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty in the past or at inclusion. Patients with a transient ischemic attack or stroke at inclusion and patients who reported stroke in the past were considered to have cerebrovascular disease. Peripheral arterial disease was defined as surgery or angioplasty of the arteries supplying the lower extremities in history or intermittent claudication or rest pain at inclusion. AAA was defined as present (distal aortic diameter ≥3 cm) or previous AAA surgery. An MRI of the brain, physical examination, and blood and urine sampling were performed. Risk factors, medical history, and functioning were assessed with questionnaires. Between January 2006 and May 2009, all living participants were invited for a follow-up evaluation, including brain MRI. The SMART-MR was approved by the local ethics committee and written informed consent was obtained from all participants.

**Study sample**

Of the 718 patients participating in the follow-up evaluation, another 38 did not undergo a second MRI and 1 was excluded because lacunar infarcts could not be rated because of motion or other artefacts. Therefore, the longitudinal analyses were performed in 679 patients.

**Magnetic resonance imaging protocol**

The MR investigations were performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/TI: 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230 x 230 mm; matrix size, 180 x 256; slice thickness, 4.0 mm; no gap; 38 slices).

**Brain segmentation**

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere.11 The
segmentation program distinguishes cortical grey matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and WMHs. The results of the segmentation analysis were checked visually for the presence of infarcts and adapted if necessary to make a distinction between WMH and infarct volumes. Total brain volume was calculated by summing the volumes of grey and white matter and present volumes of WMHs and infarcts. All volumes cranial to the foramen magnum were included. Thus, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing total brain volume, sulcal volume and ventricular CSF volume.

Lacunar infarcts and white matter hyperintensities

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded regarding patient history and diagnosis. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images ≥3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images to distinguish them from WMH. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of gliosis. The location, affected flow territory, and type were scored for every infarct. Brain infarcts were categorized as cortical infarcts, lacunar infarcts, large subcortical infarcts, and infratentorial infarcts. Large subcortical infarcts were sized >15 mm and were not confluent with cortical infarcts. Lacunar infarcts were defined according to the recently published STRIVE-criteria.¹ Lacunar infarcts were defined as infarcts of 3 mm to 15 mm in diameter and located in the subcortical areas of the frontal, parietal, temporal, and occipital lobes, corona radiate and semioval centre (defined as within deep white matter); internal capsule, thalamus, or basal ganglia (defined as basal ganglia). Infratentorial infarcts were located in the brainstem or cerebellum, irrespective of size. Periventricular lesions were defined as WMH adjacent to or within 1 cm of the lateral ventricles in both hemispheres. Deep lesions were located in the deep white matter tracts and may or may not have adjoined periventricular lesions. Volumes of WMH were normalized for ICV and expressed as percentage of ICV.

Vascular risk factors

On both visits, an overnight fasting venous blood sample was taken to determine glucose, lipid, creatinine and total plasma homocysteine levels (THCY). Hyperhomocysteinemia was defined according to sex-specific 95th percentiles as a fasting THCY level of 16.3 μmol/L or greater.
in women and 18.8 μmol/L or greater in men.\textsuperscript{12} Height and weight were measured without shoes and heavy clothing, and the body mass index (BMI) was calculated (kg/m\textsuperscript{2}). Systolic and diastolic blood pressures (mm Hg) were measured twice with a sphygmomanometer and averaged. Presence was of hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, use of antihypertensive medication or history of hypertension. Diabetes mellitus was defined as a glucose level of ≥7.0 μmol/L or self-reported use of oral antidiabetic drugs or insulin. Smoking status was expressed in packyears and alcohol intake was categorized as never, former, or current. An ECG was performed at baseline to assess the presence of atrial fibrillation. Ultrasonography was performed to measure intima-media thickness (IMT) (mm) in the left and right common carotid arteries, represented by the mean value of six measurements and to assess carotid stenosis.

**Data analysis**

We used multiple imputation (10 datasets) to address missing values\textsuperscript{13} in the study population using the statistical programme R (aregImpute) (version 2.10.0). Data were analysed using SPSS version 17.0 (Chicago, Ill, USA), by pooling the 10 imputed datasets. First, baseline characteristics were calculated for the study sample (n=679). New lacunar infarcts were defined as 1 or more new lacunar infarcts on follow-up MRI.

Second, we calculated the proportions of patients with risk factors in the groups without new lacunar infarcts, with new lacunar infarcts only in the deep white matter, with new lacunar infarcts only in the basal ganglia and with new lacunar infarcts in both localisations. We performed chi square testing and ANOVA testing with bonferroni correction to test for between-group differences.

Third, for the association between baseline presence of vascular risk factors and new lacunar infarcts in deep white matter and basal ganglia at follow-up, we used Poisson regression models with log-link function and robust standard errors to estimate relative risks (RR) and accompanying confidence intervals (CI) rather than odds ratios which tend to overestimate the relative risk.\textsuperscript{14,15} Analyses were performed to estimate the association of presence of hypertension, diabetes, cholesterol level, hyperhomocysteinemia, packyears of smoking, baseline WMH volume, progression of WMH volume (defined as highest quintile of change at follow-up), carotid stenosis ≥70%, and atrial fibrillation with risk of new lacunar infarcts in deep white matter or basal ganglia, respectively, as outcome variable, adjusted for age and sex (model 1). Secondly, we adjusted for baseline WMH volume (% of ICV), as it is possible that lacunar infarcts present as WML and cavitate over time\textsuperscript{16} or new lacunar
infarcts develop within pre-existent white matter hyperintensities (model 2). Finally, all analyses were repeated after adjusting for all vascular risk factors (model 3).

RESULTS

Baseline characteristics of the study sample are shown in Table 9.1. At baseline, lacunar infarcts in the deep white matter were present in 12% and lacunar infarcts in the basal ganglia in 9% of the patients. A total of 257 lacunar infarcts were counted at baseline, 168 (65%) of which were in the deep white matter and 89 (35%) in the basal ganglia. In patients with severe WML on baseline (n=140), 21% had lacunar infarcts in basal ganglia and 29% had lacunar infarcts in the deep white matter. After a mean follow-up of 3.9 years, we counted 68 new lacunar infarcts in the deep white matter in 37 (6%) patients, and 66 new lacunar infarcts in the basal ganglia in 44 (7%) patients. Eleven patients had both new infarcts in the deep white matter and the basal ganglia.

Table 9.1  Baseline characteristics of the follow-up study sample (n=679)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57.5 (9.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>81.6</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Smoking (packyears)*</td>
<td>19.8 (0–49)</td>
</tr>
<tr>
<td>Present alcohol use (%)</td>
<td>79</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>140 (20)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82 (10)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.8 (1.0)</td>
</tr>
<tr>
<td>Homocysteine level (µmol/l)</td>
<td>13.2 (4.3)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Macrovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>23</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>62</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>18</td>
</tr>
<tr>
<td>Intima-media thickness (mm)</td>
<td>0.92 (0.30)</td>
</tr>
<tr>
<td>Cerebral small vessel disease</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarcts in deep white matter (%)</td>
<td>12</td>
</tr>
<tr>
<td>Lacunar infarcts in basal ganglia (%)</td>
<td>9</td>
</tr>
<tr>
<td>White matter lesion volume (ml)*</td>
<td>1.4 (0.41–6.1)</td>
</tr>
</tbody>
</table>

* Median value (10th–90th percentile).
Longitudinal analyses

The proportion of patients with several vascular risk factors for the different groups of patients (no new lacunar infarcts, new infarcts only in deep white matter, new infarcts only in basal ganglia, new infarcts in both localisations) are shown in Table 9.2. Almost all vascular risk factors were more prevalent in patients with lacunar infarcts in either anatomical territory, with some (history of CVD, hyperhomocysteinemia, hypertension and baseline WMH volume) even more prevalent in the group of patients with new LIs in both anatomical territories.

Lacunar infarcts in deep white matter

Age (RR=1.7, 95% CI 1.2 to 2.4), history of cerebrovascular disease (RR=2.5, 1.3 to 5.0), hypertension (RR=3.4, 1.2 to 9.7), presence of carotid stenosis ≥70% (RR=2.5, 1.2 to 5.0), smoking (per packyear RR=1.02, 1.01 to 1.03) and progression of WMH volume (RR=2.4, 1.1

Table 9.2  Proportions of patients with vascular risk factor according to presence and localisation of new lacunar infarcts at follow-up

<table>
<thead>
<tr>
<th></th>
<th>No new lacunar infarcts (n=609)</th>
<th>New lacunar infarcts in basal ganglia (n=33)</th>
<th>New lacunar infarcts in deep white matter (n=26)</th>
<th>New infarcts in both localisations (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>56.8 (9.4)</td>
<td>63.8 (9.2)*</td>
<td>63.15 (7.3)*</td>
<td>62.7 (10.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>80%</td>
<td>91%</td>
<td>96%*</td>
<td>91%</td>
</tr>
<tr>
<td>History of CVD (%)</td>
<td>23%</td>
<td>42%*</td>
<td>39%*</td>
<td>82%*</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>10%</td>
<td>27%*</td>
<td>15%</td>
<td>36%*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64%</td>
<td>79%</td>
<td>89%*</td>
<td>91%</td>
</tr>
<tr>
<td>Carotid stenosis (&gt;70%)</td>
<td>9%</td>
<td>9%</td>
<td>23%*</td>
<td>27%*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
<td>28%*</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>26.8 (3.5)</td>
<td>26.3 (3.5)</td>
<td>25.4 (3.6)</td>
<td>26.5 (4.4)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L) (SD)</td>
<td>4.8 (1.0)</td>
<td>4.5 (0.8)</td>
<td>4.9 (0.8)</td>
<td>4.9 (0.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Pack years</td>
<td>21.2</td>
<td>24.7</td>
<td>28.5</td>
<td>31%</td>
</tr>
<tr>
<td>Severe WML at baseline</td>
<td>16%</td>
<td>58%*</td>
<td>50%*</td>
<td>82%*</td>
</tr>
<tr>
<td>Progression of WML</td>
<td>19%</td>
<td>36%*</td>
<td>54%*</td>
<td>46%*</td>
</tr>
</tbody>
</table>

* Significant mean difference compared to persons without new lacunar infarcts at the p<0.05 level, using chi-square testing (for proportions) and ANOVA (for means) with bonferroni correction.
to 5.2) were associated with new lacunar infarcts in deep white matter after adjustments for age, sex and baseline WMH volume (model 2) (Figure 9.1). The association for hypertension (RR=3.2, 95% CI 1.2 to 8.7) and progression of WMH volume (RR=2.2, 1.0 to 4.5) remained essentially the same after adjustment for all vascular risk factors (model 3). Hyperhomocysteinemia (Figure 9.1), smoking, cholesterol level, atrial fibrillation, diabetes and BMI (data not shown) were not significantly associated with lacunar infarcts in the deep white matter.

**Lacunar infarcts in basal ganglia**

Age (RR=1.7, 95% CI 1.2 to 2.4), history of cerebrovascular disease (RR=2.6, 1.5 to 4.7) were significantly and hyperhomocysteinemia (RR=2.0, 1.0 to 4.2, p=0.065) borderline significantly associated with new lacunar infarcts in the basal ganglia after adjustments for age, sex and baseline WMH volume (Figure 9.1). The associations with history of cerebrovascular disease (RR=2.4, 95% CI 1.3 to 4.5) and hyperhomocysteinemia (RR=2.1, 1.1 to 4.5) remained the

Figure 9.1  Risk ratios for new lacunar infarcts in basal ganglia and deep white matter at follow-up. Figure shows ORs (upper 95% CI) for new lacunar infarcts at follow-up for vascular risk factors with significant associations. Blue bar: new LI in basal ganglia, grey bar: new LI in deep white matter. Adjusted for age, sex and baseline WML volume. * p<0.05.
same after adjustment for all vascular risk factors. Hypertension, presence of carotid stenosis ≥70%, smoking, progression of WML volume (Figure 9.1), cholesterol level, atrial fibrillation, diabetes and BMI were not associated with lacunar infarcts in the basal ganglia.

**DISCUSSION**

In this study we found that age, baseline WMH and history of cerebrovascular disease increased the risk of new lacunar infarcts in both deep white matter and basal ganglia. Hyperhomocysteinemia was only significantly associated with new lacunar infarcts in the basal ganglia, independent of other vascular risk factors. In contrast, carotid stenosis >70%, smoking, hypertension and progression of WML volume were significant risk factors for new lacunar infarcts isolated to the deep white matter, the latter two independent of other vascular risk factors. The results show different vascular risk factor profiles for new lacunar infarcts in the basal ganglia and in the deep white matter.

Strengths of this study are the longitudinal design, the large sample size, and the automated volumetric assessment of WML. In addition, we visually differentiated between lacunar infarcts in deep white matter and basal ganglia. Finally, detailed assessment of vascular risk factors and atherosclerosis allowed for analyses of many vascular risk factors, including extent of atherosclerosis. Only 58% of all patients participated in the follow-up study. Patients who did not participate at follow-up were older, had higher vascular burden and had higher WMH volumes at baseline. This probably caused an underestimation of the associations. Although the longitudinal sample was relatively large, the number of new lacunar infarcts was limited, which could have resulted in a lack of power. Finally, we did not visually distinguish lacunar infarcts that appeared within pre-existent WMH at follow-up. However, we adjusted for baseline WMH volume and progression of WMH volume was clearly defined. Our analyses showed an association of progression of WMH volume with new lacunar infarcts in deep white matter independent of baseline WMH volume as opposed to lacunar infarcts in the basal ganglia, thereby supporting the hypothesis that most of these lacunar infarcts appear in pre-existent WMH or with new WMH lesions.

Limited data are available concerning risk factors for new lacunar infarcts regarding their anatomical location. Our results on lacunar infarcts in the deep white matter are partially in line with one other longitudinal study on this subject, which reported that hypertension was associated with new subcortical lacunar infarcts and that 71% of new lacunar infarcts in the subcortical white matter were surrounded by new developing white matter lesions.3
Other cross-sectional studies have also reported on an association with hypertension.\textsuperscript{17,18} Additionally, we found that carotid stenosis $>70\%$ and smoking were associated with new lacunar infarcts, although this was not independent of other vascular risk factors. This in line with one other cross-sectional study on lacunar infarcts in the deep white matter, which reported more occlusive carotid or middle cerebral artery diseases (53\% versus 19\%; $p=0.0004$), in this group.\textsuperscript{8} Interestingly, another recently published study did not find any differences in prevalence of vascular risk factors, except that patients with a lacunar infarct in the deep white matter were less likely to have an embolic source (defined as atrial fibrillation or carotid stenosis).\textsuperscript{9} In contrast to our and the other longitudinal study,\textsuperscript{3} this study was cross-sectional and only included patients with clinically apparent lacunar syndromes, whereas our study also included silent lacunar infarcts. As silent lacunar infarcts are more likely to be in the deep white matter and to be associated with cerebral small vessel disease this could possibly explain these differences.

We are not aware of data on hyperhomocysteinemia, which we found to be associated with new lacunar infarcts in the basal ganglia. Most of the basal ganglia are supplied by the lenticulostral arteries which are more prone to acute ischemic occlusion due to growing athero-thrombotic lesions or possible thrombo-emboli.\textsuperscript{6} Hyperhomocysteinemia is a known risk factor for large and small vessel disease and we speculate that its atherogenic and prothrombotic properties mostly described in large vessel disease\textsuperscript{19} could have an effect on the development of atheromatic and thrombotic lesions in the perforating arteries, which are still large enough to develop atherosclerotic lesions. This hypothesis is supported by the observation that a history of cerebrovascular disease was, independent of other vascular risk factors, only significantly associated with new lacunar infarcts in the basal ganglia.

The independent relation between progression of WMH volume and new lacunar infarcts in the deep white matter is particularly interesting. Our study and a previous one\textsuperscript{1} suggest that progression of WMH volume and new lacunar infarcts in the deep white matter have a shared aetiology. It could very well be that the majority of these types of lacunar infarcts develop within pre-existent and at the borders of developing WMH as a more overt type of ischemia with subsequent necrosis and cavitation (Figure 9.2). This hypothesis is supported by pathological evidence showing incomplete lacunar infarction as a pathological intermediate between WMH and overt lacunar infarction\textsuperscript{1} and clinical evidence that incident lacunar infarcts preferably appear at the borders of WMHs.\textsuperscript{10} The association between these two radiological abnormalities independent of other vascular risk factors also suggests that appearance of lacunar infarcts in the deep white matter can be viewed as a progressive variant of small vessel disease, whereas new lacunar infarcts in the basal ganglia may not.
The differing risk factor profiles suggest aetiological differences between lacunar infarcts in the deep white matter and the basal ganglia. The deep white matter is a watershed area supplied by the terminal vessels originating from the subarachnoid circulation on the one hand and the deep perforating (lenticulostriatal) arteries on the other hand. Arteriolosclerosis, decreased cerebral blood flow, impaired autoregulation and blood-brain barrier damage can cause hypoperfusion and subsequent ischemia in the deep white matter. Hypertension and carotid stenosis are involved in the development of arteriolosclerosis and hypoperfusion. Conversely, it is more likely that lacunar infarcts in the basal ganglia are caused by more acute infarction, such athero-thrombo-embolic closure of the (proximal) perforating arteries as opposed to the more chronic development of multiple lacunar infarcts in the deep white matter (and most often, within deep white matter hyperintensities). These findings are supported by clinical data, which show a different prognosis between patients with either singular or multiple lacunar infarcts. This possible aetiological difference could explain the large heterogeneity between study populations, with all lacunar infarcts being considered one clinical entity. We recommend distinguishing lacunar infarcts according to anatomical location in future studies to provide more information on this possible difference.

Figure 9.2  Lacunar infarcts in deep white matter at follow-up. Baseline (A) and follow-up MRI (B). Progressive WML and new LIs (arrows). Note the appearance of new infarcts in and at the borders of progressive WMHs.
REFERENCES


