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Do Lacunar Infarcts Have Different Aetiologies? Risk Factor Profiles of Lacunar Infarcts in Deep White Matter and Basal Ganglia: The Second Manifestations of ARTerial Disease-Magnetic Resonance Study

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Cerebral lacunes · Magnetic resonance imaging · Risk factors

Abstract
Background: Evidence suggests that lacunar infarcts have different etiologies, 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 Second Manifestations of ARTerial disease-Magnetic Resonance 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 association 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 white matter hyperintensity (WMH) volume were associated with increased risk of new lacunar infarcts in both locations. Hyperhomocysteinemia was associated with increased risk of lacunar infarcts in the basal ganglia (relative risk [RR] 2.0; 95% CI 1.0–4.2), whereas carotid stenosis >70% (RR 2.5; 95% CI 1.2–5.0), smoking (per 10 pack-year: RR 1.1; 95% CI 1.0–1.3), hypertension (RR 3.4; 95% CI 1.2–9.7), and progression of WMH volume (RR 2.4; 95% CI 1.1–5.2) were associated with increased risk of lacunar infarcts in the deep white matter. ***Conclusions:*** The different risk factor profiles for new lacunar infarcts in basal ganglia and deep white matter indicate different etiologies. The independent association between progression of WMH and new deep white matter lacunar infarcts suggest a common etiology for these radiological abnormalities.

Introduction

Lacunes of presumed vascular origin (lacunar infarcts), together with white matter hyperintensities (WMHs) of presumed vascular origin, are the hallmarks of cerebral small vessel disease (CSVD) [1]. They are ischemic

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lesions, identified on MRI, which can be silent or can lead to clinical symptoms [2]. It is suggested that anatomical location of lacunar infarcts is important with respect to their etiology and clinical consequences. Lacunar infarcts in the deep white matter are often clinically silent and appear in or nearby confluent WMHs [3]. It has been hypothesized that they appear gradually under the influence of chronic ischemia due to arteriolosclerosis or endothelial damage [4, 5]. In contrast, lacunar infarcts in the basal ganglia often lead to clinical symptoms, such as pure motor or sensory stroke [6, 7], because of their strategic location and larger size. 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 [2]. Risk may 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 [3, 8, 9], whereas risk factors more commonly associated with large vessel disease, such as atrial fibrillation, are associated with infarcts in the basal ganglia [3]. Only few studies reported on risk factors for lacunar infarcts in deep white matter and basal ganglia in the same population [3, 9], and only one was a longitudinal study on new infarcts [3]. We examined the longitudinal association between baseline vascular risk factors and new lacunar infarcts in the deep white matter and basal ganglia, hypothesizing that the patients with lacunar infarcts in deep white matter and basal ganglia have different risk factor profiles.

Materials 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 1,309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere [10]. 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 those 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 artifacts. Therefore, the longitudinal analyses were performed in 679 patients.

MRI 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: 2,200/11 and 2,200/100 ms), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6,000/100/2,000 ms), and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2,900/22/410 ms) (field of view 230 × 230 mm; matrix size, 180 × 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, brain stem, and cerebellum. Total intracranial volume (ICV) was calculated by summing total brain volume, sulcal volume, and ventricular CSF volume.

Lacunar Infarcts and WMHs

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. Infarcts located within WMHs also had to be hypointense on T1-weighted and FLAIR images to distinguish them from surrounding WMHs. 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 conflu-

ent with cortical infarcts. Lacunar infarcts were defined according to the STRIVE-criteria [1]. Lacunar infarcts were defined as infarcts of 3–15 mm in diameter and located in the subcortical areas of the frontal, parietal, temporal, and occipital lobes, corona radiate, and semiovale center (defined as within deep white matter); internal capsule, thalamus, or basal ganglia (defined as basal ganglia). Infratentorial infarcts were located in the brain stem or cerebellum, irrespective of size. Periventricular lesions were defined as WMH adjacent to or within 1 cm of the lateral ventricles. 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. Severe WMH volume at baseline was defined as the highest quintile of WMH volume and progression of WMH as the highest quintile of change in WMH volume.

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 [12]. Height and weight were measured without shoes and heavy clothing, and the body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured twice with a sphygmomanometer and averaged. Hypertension was defined as a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, 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 anti-diabetic drugs or insulin. Smoking status was expressed in pack-years and alcohol intake was categorized as never, former, or current. An ECG was performed at baseline to assess atrial fibrillation. Ultrasonography was performed to measure intima-media thickness (mm) in the left and right common carotid arteries, represented by the mean value of 6 measurements and to assess carotid stenosis.

Data Analysis

We used multiple imputation (10 data sets) to address missing values in the study population [13], using the statistical programme R (aregImpute; version 2.10.0). Data were analyzed using SPSS version 20.0 (Chicago, IL, 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 localizations. 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 SEs to estimate relative risks (RRs) and accompanying CI rather than odds ratios which tend to overestimate the RR [14, 15]. Analyses were performed to estimate the association of presence of hypertension, diabetes, cholesterol level, hyperhomocysteinemia, pack-years of smoking, baseline WMH volume, progression of WMH volume, 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). Second, we adjusted for baseline WMH volume (% of ICV), as it is possible that lacunar infarcts present as WMH cavitate over time [16] or new lacunar infarcts develop within pre-existent WMHs (model 2). Third, all analyses were repeated after adjusting for all vascular risk factors (model 3). Finally, as antihypertensive treatment could influence the results, we additionally adjusted for this.

Table 1. Baseline characteristics of the follow-up study sample (n = 679)

Risk factor	Study sample
Age, years	57.5 (9.6)
Male, %	81.6
Vascular risk factors	
Smoking, pack-years*	19.8 (0–49)
Present alcohol use, %	79
Systolic blood pressure, mm Hg	140 (20)
Diastolic blood pressure, mm Hg	82 (10)
Cholesterol, mmol/L	4.8 (1.0)
Homocysteine level, μmol/L	13.2 (4.3)
Diabetes, %	16
Atrial fibrillation, %	3.2
Macrovascular risk factors	
Cerebrovascular disease, %	23
Coronary artery disease, %	62
Peripheral artery disease, %	18
Intima-media thickness, mm	0.92 (0.30)
Cerebral small vessel disease	
Lacunar infarcts in deep white matter, %	12
Lacunar infarcts in basal ganglia, %	9
White matter hyperintensity volume, mL*	1.4 (0.41–6.1)

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

Results

Baseline characteristics of the study sample are shown in Table 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 WMH 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

Table 2. Proportions of patients with vascular risk factor according to presence and localization of new lacunar infarcts at follow-up

	No new lacunar infarcts (n = 609)	New lacunar infarcts in basal ganglia (n = 33)	New lacunar infarcts in deep white matter (n = 26)	New infarcts in both localisations (n = 11)
Age, years	56.8 (9.4)	**63.8 (9.2)**[a]	**63.15 (7.3)**[a]	62.7 (10.6)
Male	80	91	**96**[a]	91
History of CVD	23	**42**[a]	**39**[a]	**82**[a]
Hyperhomocysteinemia	10	**27**[a]	15	**36**[a]
Hypertension	64	**79**	**89**[a]	91
Carotid stenosis (>70%)	9	9	**23**[a]	**27**[a]
Diabetes	15	**28**[a]	27	27
BMI, kg/m^2	26.8 (3.5)	26.3 (3.5)	25.4 (3.6)	26.5 (4.4)
Cholesterol, mmol/L	4.8 (1.0)	4.5 (0.8)	4.9 (0.8)	4.9 (0.8)
Atrial fibrillation	3	6	4	0
Packyears	21.2	24.7	28.5	31
Severe WMH at baseline	16	**58**[a]	**50**[a]	**82**[a]
Progression of WMH	19	**36**[a]	**54**[a]	**46**[a]

[a] Significant mean difference compared to persons without new lacunar infarcts at the $p \leq 0.05$ level, using chi-square testing (for proportions) and ANOVA (for means) with Bonferroni correction.

CVD, cerebrovascular disease; BMI, body mass index; WMH, white matter hyperintensity; ANOVA, analysis of variance.

Values are mean (SD) or percentages.

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.

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 localizations) are shown in Table 2. Almost all vascular risk factors were more prevalent in patients with lacunar infarcts in either anatomical territory, with some even more prevalent in the group of patients with new LIs (history of CVD, hyperhomocysteinemia, hypertension, and baseline WMH volume) in both anatomical territories.

Lacunar Infarcts in Deep White Matter

All results are shown in Table 3. Age (RR 1.7; 95% CI 1.2–2.4), history of cerebrovascular disease (RR 2.5; 95% CI 1.3–5.0), hypertension (RR 3.4; 95% CI 1.2–9.7), presence of carotid stenosis ≥70% (RR 2.5; 95% CI 1.2–5.0), smoking (per 10 pack-years: RR 1.1; 95% CI 1.0–1.3), baseline WMH volume (RR 1.8; 95% CI 1.2–2.7), and progression of WMH volume (RR 2.4; 95% CI 1.1–5.2) were associated with new lacunar infarcts in deep white matter after adjustments for age, sex, and baseline WMH volume (model 2; Fig. 1). The association for hypertension (RR 3.2; 95% CI 1.2–8.7) and progression of WMH volume (RR 2.2; 95% CI 1.0–4.5) remained essentially the same after adjustment for all vascular risk factors (model 3). Hyperhomocysteinemia (Fig. 1), cholesterol level, atrial fibrillation, diabetes, and BMI (data not shown) were not significantly associated with lacunar infarcts in the deep white matter.

After adjusting for use of antihypertensive agents, only the association for hypertension increased (RR 4.2; 95% CI 1.5–12.0), suggesting that untreated patients had higher risks.

Lacunar Infarcts in Basal Ganglia

Age (RR 1.7; 95% CI 1.2–2.4), history of cerebrovascular disease (RR 2.6; 95% CI 1.5–4.7), baseline WMH volume (RR 2.0; 95% CI 1.5–2.6) were significantly and hyperhomocysteinemia (RR 2.0; 95% CI 1.0–4.2, p = 0.065) borderline significantly associated with new lacunar infarcts in the basal ganglia after adjustments for age, sex, and baseline WMH volume (Fig. 1). The associations with history of cerebrovascular disease (RR 2.4; 95% CI 1.3–4.5), hyperhomocysteinemia (RR 2.1; 95% CI 1.1–4.5), and baseline WMH volume (RR 1.9; 95% CI 1.5–2.5) remained the same after adjustment for all vascular risk factors. Hypertension, presence of carotid stenosis ≥70%,

Table 3. Relative risk for incident lacunar infarcts in deep white matter and basal ganglia during follow-up. Adjusted for age and sex (model 1), baseline WMH volume (model 2) and all additional vascular risk factors (model 3)

Risk factor	Model	New LACI in deep white matter (n = 68)	New LACI in basal ganglia (n = 66)
Age per 10 years	Model 1	1.9 (1.4–2.7)***	2.1 (1.4–2.9)***
	Model 2	1.7 (1.2–2.4)**	1.7 (1.2–2.4)**
	Model 3	1.3 (0.9–1.9)	1.5 (1.0–2.1)*
Sex, male	Model 1	3.9 (0.9–16.2)	2.2 (0.8–6.1)
	Model 2	3.6 (0.9–15.0)	2.0 (0.7–5.4)
	Model 3	3.2 (0.8–12.9)	1.7 (0.6–4.9)
History of cerebrovascular disease (yes/no)	Model 1	2.7 (1.3–5.2)**	2.7 (1.5–5.0)***
	Model 2	2.5 (1.3–5.0)**	2.6 (1.5–4.7)***
	Model 3	1.6 (0.8 to –3.5)	2.4 (1.3–4.5)**
Hypertension (yes/no)	Model 1	3.7 (1.3–10.3)*	1.9 (0.9–4.1)
	Model 2	3.4 (1.2 to –9.7)*	1.7 (0.8–5.7)
	Model 3	3.2 (1.2–8.7)*	1.7 (0.8–3.6)
Smoking	Model 1	1.01 (1.0–1.03)*	1.01 (1.0–1.02)
	Model 2	1.02 (1.01–1.03)**	1.01 (1.0–1.02)*
	Model 3	1.01 (1.0–1.03)*	1.01 (1.0–1.02)
Hyperhomocysteinemia (yes/no)	Model 1	1.8 (0.8–4.0)	2.7 (1.4–5.1)**
	Model 2	1.4 (0.5–3.7)	2.0 (1.0–4.2)
	Model 3	1.3 (0.5–3.0)	2.1 (1.1–4.2)*
Carotid stenosis >70%	Model 1	2.3 (1.1–4.8)*	1.4 (0.7–2.9)
	Model 2	2.5 (1.2–5.0)*	1.5 (0.7–3.2)
	Model 3	1.5 (0.7–3.3)	1.0 (0.4–2.3)
Progression WMH volume (yes/no)	Model 1	2.8 (1.4–5.7)**	1.5 (0.8–2.8)
	Model 2	2.4 (1.1–5.2)*	1.0 (0.5–2.1)
	Model 3	2.2 (1.0–4.5)*	0.7 (0.4–1.6)
Atrial fibrillation (yes/no)	Model 1	0.7 (0.1–5.7)	1.2 (0.4–4.0)
	Model 2	0.7 (0.1–5.5)	1.2 (0.4–3.5)
	Model 3	1.1 (0.1–9.9)	1.8 (0.6–5.5)
Diabetes (yes/no)	Model 1	1.6 (0.8–3.2)	1.6 (0.9–2.9)
	Model 2	1.5 (0.7–3.1)	1.5 (0.8–2.8)
	Model 3	1.5 (0.7–3.1)	1.3 (0.7–2.4)
Cholesterol level, mmol	Model 1	1.1 (0.8–1.5)	0.8 (0.6–1.1)
	Model 2	1.1 (0.8–1.4)	0.8 (0.6–1.0)
	Model 3	1.0 (0.8–1.5)	0.7 (0.5–1.0)
BMI, kg/m^2	Model 1	0.93 (0.81–1.06)	0.99 (0.89–1.09)
	Model 2	0.93 (0.81–1.06)	1.0 (0.90–1.10)
	Model 3	0.91 (0.80–1.03)	1.0 (0.9–1.1)
Baseline WMH volume	Model 1	1.8 (1.2–2.7)**	2.0 (1.5–2.6)***
	Model 2	na	na
	Model 3	1.5 (0.9–2.4)	1.9 (1.5–2.5)***
Pack-years (per 10 years)	Model 1	1.2 (1.0–1.3)*	1.1 (1.0–1.2)
	Model 2	1.2 (1.0–1.3)**	1.1 (1.0–1.3)*
	Model 3	1.1 (1.0–1.3)*	1.1 (1.0–1.3)

WMH, white matter hyperintensity; BMI, body mass index; LACI, lacunar infarct; na, not applicable.
* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

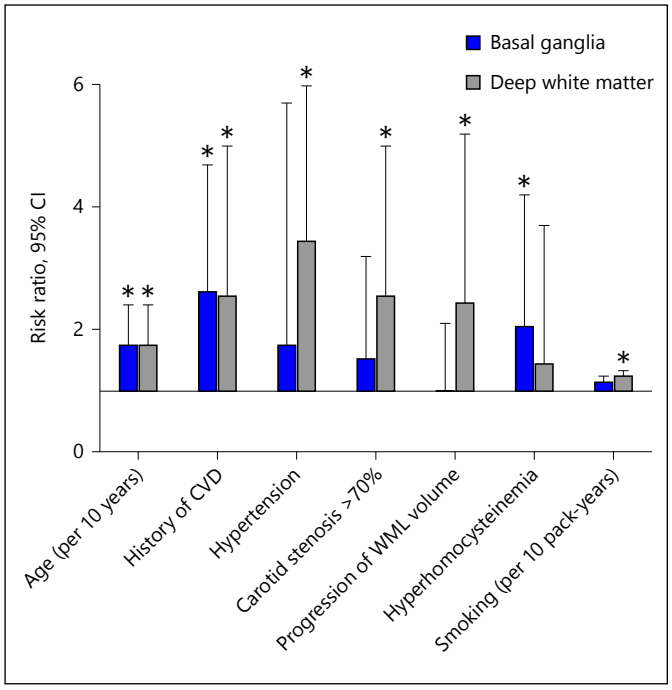

Fig. 1. Risk ratios for new lacunar infarcts in basal ganglia and deep white matter at follow-up. Figure shows ORs (upper 95% CI) for new lacunar infarcts at follow-up for vascular risk factors with significant associations. Blue bar: new LI in basal ganglia, grey bar: new LI in deep white matter. Adjusted for age, sex, and baseline white matter hyperintensity volume. * $p \leq 0.05$. CVD, cerebrovascular disease; WMH, white matter hyperintensity.

smoking, progression of WMH volume (Fig. 1), cholesterol level, atrial fibrillation, diabetes, and BMI were not associated with lacunar infarcts in the basal ganglia.

Discussion

In this study, age, baseline WMH, and history of cerebrovascular disease increased the risk of all new lacunar infarcts. 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 WMH volume were significant risk factors for new lacunar infarcts in the deep white matter, the latter 2 independent of other vascular risk factors. The results show different vascular risk factor profiles for lacunar infarcts in the basal ganglia and the deep white matter.

Strengths of this study are the longitudinal design, the large sample size, and the automated volumetric assessment of WMH. We visually rated lacunar infarcts to differentiate between lacunar infarcts in deep white matter and basal ganglia. Detailed assessment of vascular risk factors and atherosclerosis allowed for analyses of many vascular risk factors, including extent of atherosclerosis. Only 58% of patients participated in the follow-up study. Non-participants at follow-up were older, and had higher vascular burden and WMH volumes. This probably caused an underestimation of the associations. Also, our study cohort consisted of patients with pre-existent vascular disease with high prevalence of risk factors, which could hamper comparisons in the group. However, in our notion, this makes the noted differences even more interesting, as these were found despite the baseline prevalence of risk factors. 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 was clearly defined.

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 in line with one other longitudinal study, which reported that hypertension was associated with new subcortical lacunar infarcts and that 71% of these lacunar infarcts were surrounded by new WMHs [3]. Cross-sectional studies also reported on an association with hypertension [17, 18]. The importance of hypertension is emphasized considering the even higher RR of new lacunes in the deep white matter in patients with untreated hypertension. 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, which reported more occlusive carotid or middle cerebral artery diseases (53 vs. 19%; $p = 0.0004$) in lacunar infarcts in the deep white matter [8]. Interestingly, a recently published study did not find any differences in prevalence of risk factors, except that patients with a lacunar infarct in the deep white matter were less likely to have an embolic source [9]. However, 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 CSVD this could possibly explain these differences. Diabetes is known to be associated with recurrent lacunar infarction [19]; we could not find a significant association, although a doubling of diabetes occurred in patients with new lacunar infarcts. This lack of significance is probably explained by an overrepresentation of diabetes in the study group, which consisted of patients with vascular disease.

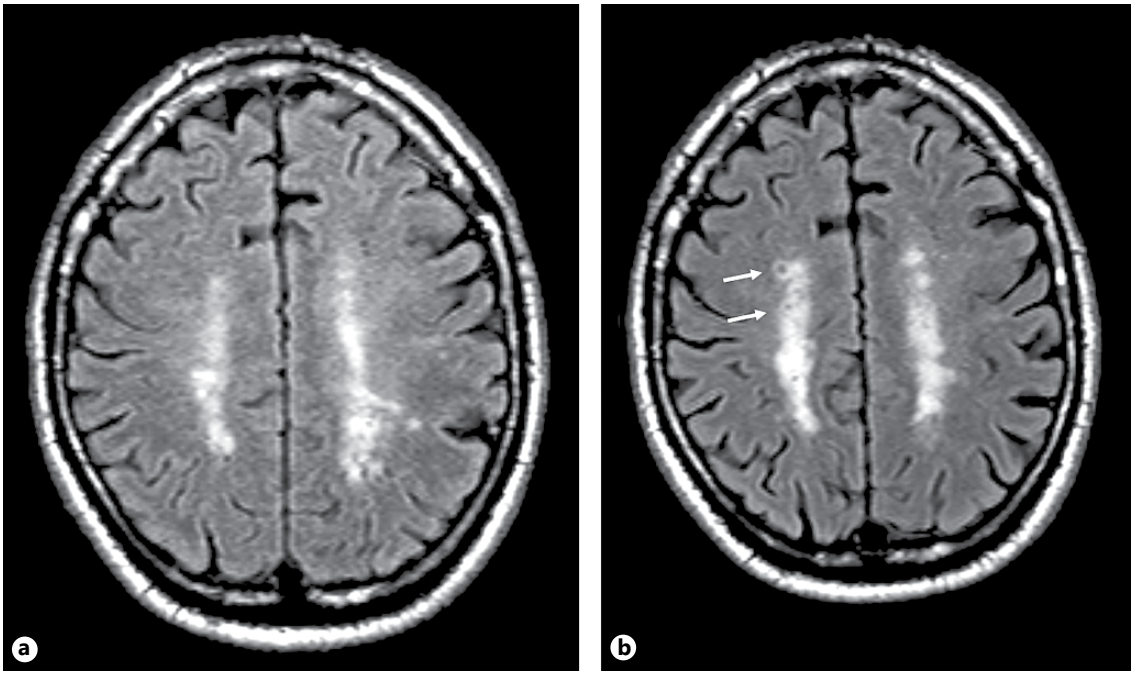

Fig. 2. Lacunar infarcts in deep white matter at follow-up. Baseline (**a**) and follow-up MRI (**b**). Progressive white matter hyperintensity (WMH) and new LIs (arrows). Note the appearance of new infarcts in and concurrent with progression of WMH.

We are not aware of data on hyperhomocysteinemia, which we found to be associated with new lacunar infarcts in the basal ganglia, although this association was weak. Most of the basal ganglia are supplied by the lenticulostriatal arteries which are more prone to acute ischemic occlusion due to growing athero-thrombotic lesions or thrombo-emboli [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 [20] could have an effect on the development of atheromic and thrombotic lesions in the perforating arteries, which are still large enough to develop atherosclerotic lesions. This 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 association between progression of WMH volume and new lacunar infarcts in the deep white matter is particularly interesting. Our study and a previous one [3] suggest that progression of WMH volume and new lacunar infarcts in the deep white matter have a shared etiology. 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 (Fig. 2). This hypothesis is supported by pathological evidence showing incomplete lacunar infarction as a pathological intermediate between WMH and overt lacunar infarction [5] and incident lacunar infarcts appearing at the borders of WMHs [21]. The association between these 2 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 etiological 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 [22]. 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. These findings are supported by clinical data, which show a different prognosis between patients with either singular or multiple lacunar infarcts [23, 24]. This possible etiological difference could explain the large heterogeneity between study populations, in which all lacunar infarcts are considered one clinical entity. An interesting focus in this regard for future clinical studies should concern cognitive impairment as this an essential clinical feature of CSVD [25]. We recommend distinguishing lacunar infarcts according to anatomical location in future studies to provide more information on this possible difference.

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