ARTICLE

The role of small diffusion-weighted imaging lesions in cerebral small vessel disease

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Abstract

Objective

To investigate the prevalence of asymptomatic diffusion-weighted imaging–positive (DWI+) lesions in individuals with cerebral small vessel disease (SVD) and identify their role in the origin of SVD markers on MRI.

Methods

We included 503 individuals with SVD from the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) study (mean age 65.6 years [SD 8.8], 56.5% male) with 1.5T MRI in 2006 and, if available, follow-up MRI in 2011 and 2015. We screened DWI scans (n = 1,152) for DWI+ lesions, assessed lesion evolution on follow-up fluid-attenuated inversion recovery, T1 and T2* images, and examined the association between DWI+ lesions and annual SVD progression (white matter hyperintensities [WMH], lacunes, microbleeds).

Results

We found 50 DWI+ lesions in 39 individuals on 1,152 DWI (3.4%). Individuals with DWI+ lesions were older ($p = 0.025$), more frequently had a history of hypertension ($p = 0.021$), and had a larger burden of preexisting SVD MRI markers (WMH, lacunes, microbleeds: all $p < 0.001$) compared to individuals without DWI+ lesions. Of the 23 DWI+ lesions with available follow-up MRI, 14 (61%) evolved into a WMH, 8 (35%) resulted in a cavity, and 1 (4%) was no longer visible. Presence of DWI+ lesions was significantly associated with annual WMH volume increase and yearly incidence of lacunes and microbleeds (all $p < 0.001$).

Conclusion

Over 3% of individuals with SVD have DWI+ lesions. Although DWI+ lesions play a role in the progression of SVD, they may not fully explain progression of SVD markers on MRI, suggesting that other factors than acute ischemia are at play.

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Glossary

CAA = cerebral amyloid angiopathy; **CI** = confidence interval; **DTI** = diffusion tensor imaging; **DWI+** = diffusion-weighted imaging–positive; **FLAIR** = fluid-attenuated inversion recovery; **ICV** = intracranial volume; **MD** = mean diffusivity; **MMSE** = Mini-Mental State Examination; **RUN DMC** = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; **STRIVE** = Standards for Reporting Vascular Changes on Neuroimaging; **SVD** = small vessel disease; **VIF** = variance inflation factor; **WMH** = white matter hyperintensities.

Cerebral small vessel disease (SVD) is the most important vascular contributor to dementia.[1,2] MRI markers of SVD include white matter hyperintensities (WMH), lacunes, and microbleeds.[3] It is generally assumed that chronic hypoperfusion plays a role in the etiology of SVD, although this has never been proven in longitudinal studies.[4,5]

Previous cross-sectional evidence has suggested that diffusion-weighted imaging–positive (DWI+) lesions representing acute ischemia are associated with SVD.[6–9] DWI+ lesions may be clinically silent, with a prevalence ranging from <1% in the general population[10,11] to 8% in patients with hypertensive SVD and up to 23% in individuals with cerebral amyloid angiopathy (CAA).[6–9] However, the role of DWI+ lesions in SVD progression remains unclear.

Recent longitudinal studies have suggested that DWI+ lesions might evolve into a spectrum of SVD markers, including a WMH, lacune, or microbleed.[12–14] However, these recent studies were small, had a short duration of follow-up, or did not investigate the whole SVD spectrum. Therefore the contribution of DWI+ lesions to the progression of SVD markers during long-term follow-up remains unknown.

Our aims were (1) to investigate the prevalence of DWI+ lesions in individuals with SVD and (2) to identify their role in the origin of the spectrum of SVD MRI markers by capturing evolution of the DWI+ lesions during a 9-year follow-up and (3) by examining the relation between the occurrence of DWI+ lesions and progression of MRI markers of SVD within this time period.

Methods

Study population

We selected 503 participants with SVD aged between 50 and 85 years from the prospective Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) study.[15] The clinical manifestation of SVD can present in acute (e.g., TIA or lacunar syndromes) and subacute form (e.g., cognitive and motor impairment).[16] However, we based the selection of participants on MRI markers of SVD including WMH or lacunes, as clinical symptoms of SVD are often diverse with a subtle onset.

Participants were excluded if they had dementia, (psychiatric) disease interfering with testing or follow-up, SVD mimics, or MRI contraindications including known claustrophobia. We included all 503 participants with MRI at baseline, of which 361 participants underwent a first follow-up MRI examination (follow-up interval 5.4 years [range 4.6–6.2]) and 296 individuals underwent a second follow-up (follow-up interval 3.4 years [range 2.7–4.1]; figure 1).

Standard protocol approvals, registrations, and patient consents

The Medical Review Ethics Committee Region Arnhem–Nijmegen approved the study, and all participants gave written informed consent.

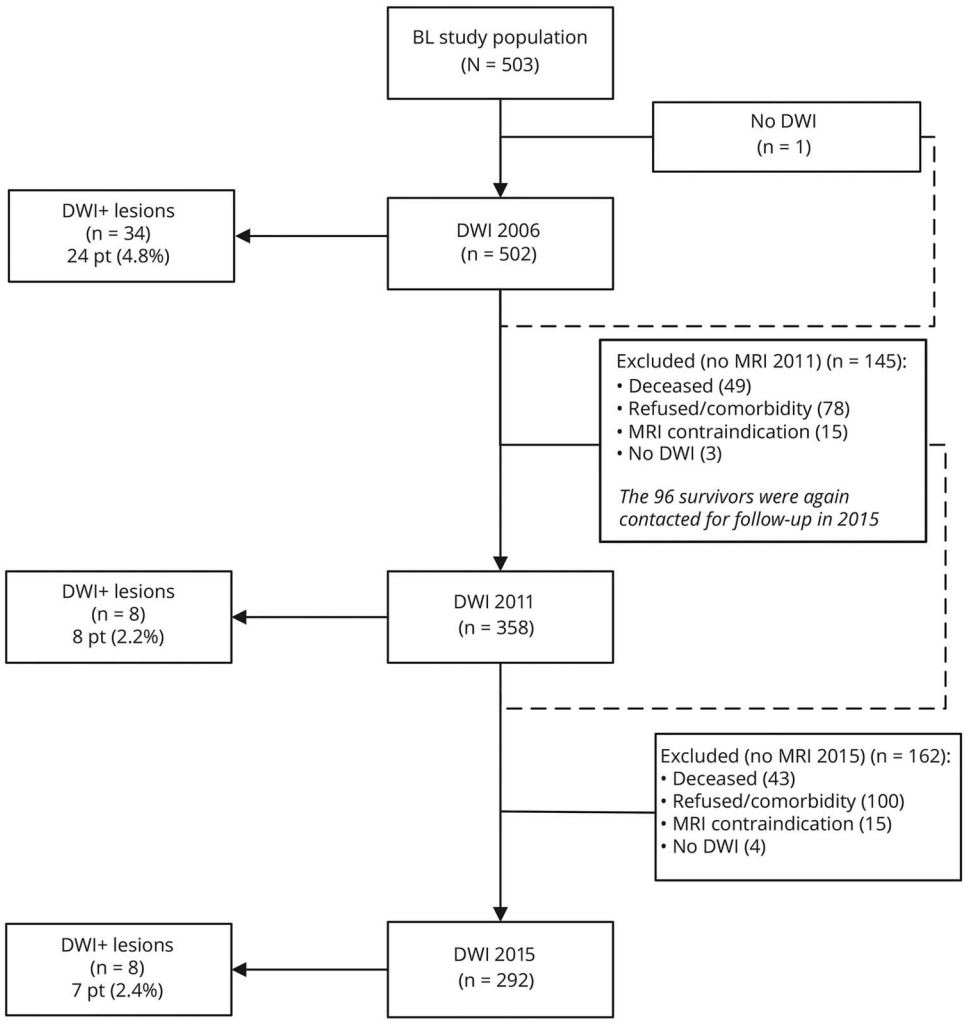
Magnetic resonance imaging

All images were collected on a 1.5T MRI system (2006: Siemens [Munich, Germany], Magnetom Sonata; 2011 and 2015: Siemens, Magnetom Avanto), using the same head coil. Acquisition details have been described previously.[15,17] In short, the following whole-brain scans were included: 3D T1 magnetization-prepared rapid gradient echo imaging (voxel size 1.0 × 1.0 × 1.0 mm); fluid-attenuated inversion recovery (FLAIR) pulse sequences (2006: voxel size 0.5 × 0.5 × 5.0 mm, interslice gap 1.0 mm; 2011 and 2015: voxel size 0.5 × 0.5 × 2.5 mm, interslice gap 0.5 mm); diffusion-weighted sequence designed for diffusion-tensor imaging (voxel size 2.5 × 2.5 × 2.5 mm, 4 unweighted scans, 30 diffusion-weighted scans, b-value 900 s/mm^{-2}); and a transversal T2*-weighted gradient echo sequence (voxel size 1.3 × 1.0 × 5.0 mm, interslice gap 1.0 mm).

Detection of DWI+ lesions and their time course

Preprocessing of diffusion data have been described previously.[15] This included correction for eddy current-induced distortions and participant motion using an in-house developed algorithm and echoplanar imaging distortion correction by means of normalization to the T1 image in the phase-encoding direction.[18] We used the diffusion data to calculate mean diffusivity (MD) images and trace images based on the geometric mean of all diffusion-weighted images. DWI indicative of DWI+ lesions were selected by a blinded rater (P.B.O.). The intensity of MD maps at the corresponding location was noted (hypointense, isointense, or hyperintense) and interpreted as lesion age.[19] Interrater agreement with an experienced and trained rater (K.W.) in a random sample of 5% (n = 58) showed excellent agreement (Cohen κ = 0.8, 95% confidence interval [CI] 0.5–1.0). Subsequently, identified DWI+ lesions were confirmed as

Figure 1 Flowchart of the study population and prevalence of diffusion-weighted imaging–positive (DWI+) lesions



N represents number of DWI+ lesions. BL = baseline; pt = participants.

definite lesions by 2 stroke neurologists (A.M.T. and F.-E.d.L.). Lesions were excluded if hyperintense on DWI scans at more than one time point as this implied most likely a T2 shine-through, hypointense on initial T2* scans suggesting microbleed-related susceptibility artifacts, or if any clinical symptoms were reported as we aimed to include clinically silent DWI+ lesions.

The appearance of the lesion on follow-up imaging was assessed by 2 experienced raters in consensus (K.W. and A.t.T.) on available FLAIR, T1, T2, and T2*-weighted sequences coregistered to the individual's DWI scan at the time of the lesion. Prior to coregistration, all images were skull-stripped using the Brain Extraction Tool from the FMRIB Software Library.[20] Using the FSL Linear Image Registration Tool (cost, mutual info), we coregistered brain-extracted T1 images to diffusion tensor imaging (DTI) space and subsequently used the computed coregistration measures to coregister FLAIR, T2, and T2* images to DTI space. All images were visually checked for coregistration errors.

Other neuroimaging markers

SVD markers were annotated according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria.[3] WMH volumes were segmented by a semiautomatic in-house developed tool,[21] visually adjusted for errors by one trained rater (I.W.M.v.U.), and normalized to baseline intracranial volume (ICV) as calculated by SPM12 (fil.ion.ucl.ac.uk/spm/software/spm12/). Number and location of lacunes and microbleeds were rated manually on FLAIR/T1-weighted and T2*-weighted images by 2 trained raters (I.W.M.v.U. and M.I.B.) blinded to clinical data. Interrater and intrarater reliabilities were excellent (weighted $\kappa \geq 0.85$ in a random sample of 10%).[22] ICV was calculated by adding gray matter volume, white matter volume, and CSF volume.

Vascular risk factors

We assessed the presence of vascular risk factors through standardized structured questionnaires and physical examination, including smoking, hypertension, body mass index, diabetes, and hypercholesterolemia, as described previously.[15]

Statistical analysis

Statistical analyses were performed in R (version 3.2.2). We compared participants with or without DWI+ lesions regarding demographics, vascular risk factors, and SVD imaging markers. We used independent sample *t* tests for group comparisons of normally distributed data and the Wilcoxon rank sum test (Mann-Whitney *U* test) for non-normally distributed data (age, WMH volume, and scores on the Mini-Mental State Examination [MMSE]). We used the Fisher exact test for group comparisons of categorical data.

We investigated the relation between DWI+ lesions and annual SVD progression by linear regression analyses (model 1) using R function lm (Package stats version 3.2.4). We defined annual SVD progression as the increase in WMH volume, number of lacunes or microbleeds over the available follow-up period divided by the number of follow-up years. We used multivariable linear regression analysis to account for possible age-related effects (model 2). Subsequently, we assessed the relations between DWI+ lesions and SVD progression, adjusting for preexisting WMH volume, number of lacunes, and number of microbleeds at the time of the DWI+ lesion (model 3).

Finally, we calculated the variance inflation factor (VIF) to assess multicollinearity among predictors in model 3, as DWI+ lesions have been shown to evolve into WMH, lacunes, and microbleeds over time. The individual VIF values for preexisting SVD markers were all below 2.5 (WMH = 1.3, lacunes = 1.1, microbleeds = 1.2). We therefore concluded that multicollinearity was unlikely.[23]

Two-tailed p values <0.05 were considered statistically significant. Data analysis was completed from January 2017 to June 2018.

Data availability

Data from the RUN DMC study including data supporting the findings of this study are available from the corresponding author on request.

Results

The 503 participants had a mean age of 65.6 years (SD 8.8) and 284 were male (56.5%). In total, 1,152 DWI scans were collected over the 3 different time points and assessed for DWI+ lesions. A total of 39 participants had one or more DWI+ lesion at any MRI time point (39/1,152; 3.4%; figure 1). We identified 50 DWI+ lesions, of which 38 were located in the white matter, 3 in the cortex, 4 in the deep gray matter, 2 in the cerebellum, and 3 overlapped both the white matter and cortex. The MD signal values at lesion locations were hypointense (n = 16) or isointense (n = 28) in most cases, suggesting that these lesions were caught in the acute phase.[19] Six lesions were captured in the subacute phase indicated by a hyperintensity on MD scans, which can typically be detected within a few weeks after the event.[24]

Differences between participants with and without DWI+ lesions

Baseline demographics, vascular risk factors, and SVD imaging markers in participants with and without DWI+ lesions are summarized in table 1. Participants with at least 1 DWI+ lesion at any MRI time point (n = 39) were older than participants without any DWI+ lesions ($p = 0.025$) but groups did not differ in sex, educational level, or MMSE score, although a negative trend was observed for a lower MMSE in individuals with a DWI+ lesion ($p = 0.052$). Moreover, individuals with a DWI+ lesion had a higher WMH volume and more frequently a lacune or microbleed (all $p < 0.001$) at baseline. The proportion of individuals with hypertension was higher in the group with a DWI+ lesion ($p = 0.021$), whereas other vascular risk factors did not differ significantly between groups.

Evolution of DWI+ lesions

Follow-up imaging for assessment of lesion evolution was available for 23 out of 50 DWI+ lesions. On first and (if available) second follow-up MRI, 22 (out of the 23 DWI+ lesions) converted to MRI markers of SVD at the exact location of the former DWI+ lesion (table 2). One lesion was no longer visible on the second MRI 5 years later. These 22 markers of SVD on follow-up appeared as a WMH in 14, whereas 8 lesions were visible as a cavity (figure 2, A and B). Of the 8 cavity lesions, 2 were smaller than the standard size for a lacune of presumed vascular origin (3–15 mm) as described in the STRIVE criteria, whereas the remaining 6 lesions did meet these criteria.[3] One DWI+ lesion that evolved into a cavity smaller than a lacune was located next to a hypointensity on T2*-weighted MRI, which remained visible on follow-up MRI, suggesting mixed (hemorrhagic and ischemic) pathology (figure 2C).

DWI+ lesions and SVD progression

Participants with DWI+ lesions at either the first or second MRI (n = 16) had a higher annual WMH progression (β = 0.173, 95% CI 0.072–0.274, $p < 0.001$), a higher yearly increase in the number of lacunes (β = 0.229, 95% CI 0.130–0.328, $p < 0.001$), and a higher yearly increase in the number of microbleeds (β = 0.275, 95% CI 0.176–0.375, $p < 0.001$) compared with individuals without DWI+ lesions (model 1; table 3). These associations remained statistically significant after adjusting for age at the time of the DWI+ lesion (model 2; table 3). The associations between the presence of DWI+ lesions and WMH progression or progression of lacunes were no longer significant after correction for preexisting WMH volume or preexisting lacunes. In contrast, the association between the presence of DWI+ lesions with the yearly increase in the number of microbleeds remained statistically significant after adjusting for the number of preexisting microbleeds (model 3; table 3).

Table 1 Baseline differences between participants with and without diffusion-weighted imaging–positive (DWI+) lesions

	DWI−	DWI+	*p* Value
No.	464	39	
Demographics			
Age, y	65.4 ± 8.8	68.8 ± 8.1	0.025
Male	266 (57)	18 (47)	0.239
Educational level, y	4.8 ± 1.4	5.0 ± 1.2	0.452
MMSE	29 (27–29)	28 (27–29)	0.057
Risk factors			
Hypertension	334 (72)	34 (89)	0.021
Diabetes	61 (13)	3 (8)	0.454
Hypercholesterolemia	219 (47)	17 (45)	0.867
Smoking ever	328 (71)	25 (66)	0.580
BMI, kg/m^2	26.7 (24.2–29.8)	26.0 (24.0–30.4)	0.617
SVD imaging markers			
WMH volume, mL	3.2 (1.2–10.2)	15.2 (6.9–24.2)	<0.001
Lacunes presence	109 (23)	23 (61)	<0.001
Microbleed presence	63 (14)	20 (53)	<0.001

Abbreviations: BMI = body mass index; MMSE = Mini-Mental State Examination; SVD = small vessel disease; WMH = white matter hyperintensities.
Data are presented as mean (SD), median (interquartile range), or n (%). Groups represent participants with at least one DWI+ lesion at any MRI time point (DWI+) or no DWI+ lesion (DWI−).

Discussion

This study shows that DWI+ lesions occur in over 3% of individuals with SVD and evolve into a WMH in around two-thirds and into a cavity in the remaining one-third of individuals. DWI+ lesions are strongly related to the presence and annual progression of SVD markers on MRI.

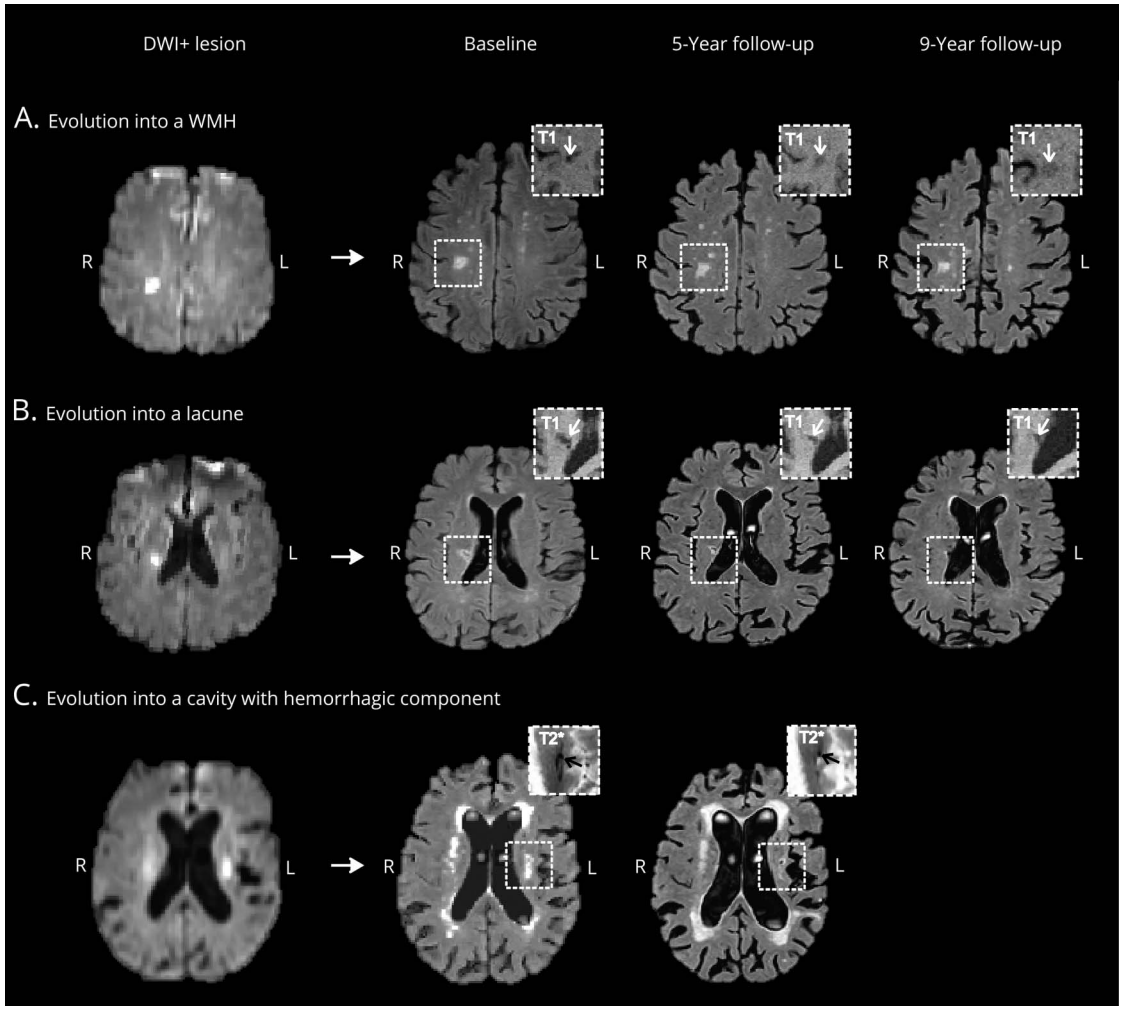
The prevalence of DWI+ lesions of 3.4% is low when compared to a previous study that found 6 DWI+ lesions in 8% of patients with hypertensive SVD.[9] This discrepancy may be explained by the fact that in this study participants had more severe SVD than in our study. We found that individuals with DWI+ lesions had a greater SVD burden at baseline (WMH volume, lacunes, microbleeds) than those without. Prevalence of DWI+ lesions indeed seems to vary according to disease severity as it ranges from virtually zero in healthy indviduals[11] up to 38% in individuals with severe manifestations of SVD such as acute ICH.[25,26] In our study, we expected DWI+ lesions to be a rare phenomenon, as individuals had predominantly mild to moderate SVD.

Table 2 Evolution of diffusion-weighted imaging-positive (DWI+) lesions by location

DWI+ lesions			Evolution into SVD markers		
Location	**N (pt)**	**FU available**	**WMH**	**Cavity**	**Disappearance**
Cortex	3 (3)	0	NA	NA	NA
Supratentorial WM	38 (28)	20 (13)	13 (9)	6 (6)	1 (1)
Overlapping (cortex and WM)	3 (3)	1 (1)	1 (1)	0	0
Deep GM	4 (4)	1 (1)	0	1 (1)	0
Cerebellum	2 (2)	1 (1)	0	1 (1)	0

Abbreviations: FU = follow-up; GM = gray matter; NA = not applicable; WM = white matter; WMH = white matter hyperintensities.
Data are presented as N (pt), where N represents the number of DWI+ lesions and pt the number of participants.

Figure 2 Evolution of diffusion-weighted imaging–positive (DWI+) lesions into a spectrum of small vessel disease MRI markers



DWI+ lesions are shown on diffusion-weighted images, whereas lesion evolution is illustrated on fluid-attenuated inversion recovery images. The insets display T1 (A, B) or T2* images (C). (A) Evolution of a DWI+ lesion into a white matter hyperintensity at 5 and 9 years of follow-up (FU). (B) Evolution of a DWI+ lesion into a lacune at 5 and 9 years of FU. Note that at the time of the DWI+ lesion cavitation is already visible. (C) A DWI+ lesion evolving into a cavity after 5 years of FU with a hemorrhagic component that was already visible at the time of the DWI+ lesion.

Preliminary evidence suggests that acute ischemia, as reflected by DWI+ lesions, plays a role in the origin of SVD markers (WMH, lacunes, microbleeds).[12–14] This is in line with our findings demonstrating that DWI+ lesions evolve into a WMH or a lacune over a follow-up period of 9 years. We did not find a DWI+ lesion evolving into a microbleed, but this may be because of small numbers. Almost all DWI+ lesions (>95%) converted into markers of SVD on follow-up, whereas in a previous small study approximately half of DWI+ lesions became radiologically inapparent after almost 7 months.[27] However, this study was small and performed in individuals with CAA. It is as yet unclear what causes a DWI+ lesion to disappear, to cavitate, or to evolve into a WMH on follow-up. Recently the severity of the ischemia corresponding to the DWI+ lesion, defined as more pronounced DWI abnormalities (lower lesional apparent diffusion coefficient values) and higher neurofilament light chain protein serum levels (a marker of neuroaxonal damage), were found to be associated with subsequent cavitation.[13]

Although DWI+ lesions seem to play a role in the origin of SVD MRI markers, they may not account for the entire progression of SVD markers on MRI. In fact, the etiology of SVD might be more heterogeneous than previously thought.[5] For instance, almost all DWI+ lesions converted into a focal, isolated WMH rather than that they were expansions of preexisting WMH, suggesting that the progression of preexisting WMH might be due to another pathologic process than that of the development of isolated, focal WMH, such as chronic hypoperfusion.[28] Similarly, recent studies showed a heterogeneous origin of microbleeds, where the majority reflected primary hemorrhages whereas some microbleeds were secondary to a microinfarct.[14,29] Despite the fact that we could not capture the conversion of a DWI+ lesion into a microbleed in this

Table 3 Associations between diffusion-weighted imaging–positive (DWI+) lesions and annual progression of small vessel disease (SVD) in individuals with DWI+ lesions at either the first or second MRI (n = 16)

	WMH volume progression, mL			Lacunes, incidence, number			Microbleeds, incidence, number		
	β	95% CI	*p* Value	β	95% CI	*p* Value	β	95% CI	*p* Value
Model 1									
DWI+ lesion	0.173	0.072 to 0.274	<0.001	0.229	0.130 to 0.328	<0.001	0.275	0.176 to 0.375	<0.001
Model 2									
DWI+ lesion	0.153	0.058 to 0.248	0.002	0.221	0.122 to 0.320	<0.001	0.258	0.159 to 0.356	<0.001
Model 3									
DWI+ lesion	−0.006	−0.087 to 0.076	0.892	0.053	−0.035 to 0.142	0.237	0.127	0.027 to 0.226	0.013

Abbreviations: β = standardized beta; CI = confidence interval; WMH = white matter hyperintensities.
Model 1 is univariable; model 2 is adjusted for age; model 3 is adjusted for age and preexisting SVD (WMH volume, number of lacunes or number of microbleeds) at the time of the DWI+ lesion.

study, we did show that DWI+ lesions were associated with annual progression of microbleeds even after adjusting for the previous number of microbleeds. Future studies should further specify the origin of MRI-defined SVD markers.

One of the strengths of this study includes the large cohort of participants with SVD with high external validity for patients with SVD from a general neurology outpatient clinic. Moreover, MRI assessment at 3 different time points allowed us to investigate the MRI signature of DWI+ lesions at multiple moments in time. Furthermore, we used a long-term follow-up period of 9 years to investigate the role of DWI+ lesions in the origin of SVD MRI markers.

Our study also has limitations. Because we were not able to make use of high field strength and high spatial resolution MRI, we may have missed DWI+ lesions <2 mm typically located in cortical regions.[30] In addition, we used interscan intervals of several years, which may have resulted in underestimation of the role of DWI+ lesions in the progression of SVD as DWI+ lesions are only visible for several weeks.[19,31] Finally, there was a selective loss to follow-up. Participants lost to follow-up were older, had a higher burden of SVD, and had more vascular risk factors compared to individuals who remained in the study, probably leading to an underestimation of DWI+ lesion occurrence and SVD progression. The generalizability of our findings to the general population might be limited as we selected participants with presence of SVD on neuroimaging.

Our study shows that over 3% of individuals with SVD have DWI+ lesions at a random MRI not related to clinical symptoms. Although DWI+ lesions play a role in SVD progression, they probably do not explain all progression of SVD markers on MRI, suggesting that other factors than acute ischemia are at play. Future high-frequency imaging studies with such short MRI intervals that they are able to capture all occurring DWI+ lesions are needed to determine to what extent DWI+ lesions can explain SVD progression, and whether they represent a promising target for future clinical trials or treatments aimed at slowing SVD progression.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Author contributions

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Annemieke ter Telgte, MSc	Radboud University Medical Center, Nijmegen, the Netherlands	Author	Contributed to data acquisition and analysis, revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Role	Contribution
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References

1. Pantoni L, Fierini F, Poggesi A, LADIS Study Group. Impact of cerebral white matter changes on functionality in older adults: an overview of the LADIS Study results and future directions. Geriatr Gerontol Int 2015;15:10–16.
2. Dichgans M, Leys D. Vascular cognitive impairment. Circ Res 2017;120:573–591.
3. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838.
4. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. J Cereb Blood Flow Metab 2016;36:1653–1667.
5. Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol 2018;14:387–398.
6. Kimberly WT, Gilson A, Rost NS, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. Neurology 2009;72:1230–1235.
7. Auriel E, Gurol ME, Ayres A, et al. Characteristic distributions of intracerebral hemorrhage-associated diffusion-weighted lesions. Neurology 2012;79:2335–2341.
8. Gregoire SM, Charidimou A, Gadapa N, et al. Acute ischaemic brain lesions in intracerebral haemorrhage: multicentre cross-sectional magnetic resonance imaging study. Brain 2011;134:2376–2386.
9. O'Sullivan M, Rich PM, Barrick TR, Clark CA, Markus HS. Frequency of subclinical lacunar infarcts in ischemic leukoaraiosis and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. AJNR Am J Neuroradiol 2003;24:1348–1354.
10. Saini M, Suministrado MS, Hilal S, et al. Prevalence and risk factors of acute incidental infarcts. Stroke 2015;46:2722–2727.
11. Batool S, O'Donnell M, Sharma M, et al. Incidental magnetic resonance diffusion-weighted imaging-positive lesions are rare in neurologically asymptomatic community-dwelling adults. Stroke 2014;45:2115–2117.
12. Conklin J, Silver FL, Mikulis DJ, Mandell DM. Are acute infarcts the cause of leukoaraiosis? Brain mapping for 16 consecutive weeks. Ann Neurol 2014;76:899–904.
13. Pinter D, Gattringer T, Enzinger C, et al. Longitudinal MRI dynamics of recent small subcortical infarcts and possible predictors. J Cereb Blood Flow Metab Epub 2018 May 8.
14. van Veluw SJ, Lauer A, Charidimou A, et al. Evolution of DWI lesions in cerebral amyloid angiopathy: evidence for ischemia. Neurology 2017;89:2136–2142.
15. van Norden AG, de Laat KF, Gons RA, et al. Causes and consequences of cerebral small vessel disease. The RUN DMC study: a prospective cohort study. Study rationale and protocol. BMC Neurol 2011;11:29.
16. Román GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426–436.
17. van Leijsen EMC, Tay J, van Uden IWM, et al. Memory decline in elderly with cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy. Hippocampus 2019:29:500–510.
18. Zwiers MP. Patching cardiac and head motion artefacts in diffusion-weighted images. Neuroimage 2010;53:565–575.
19. Lansberg MG, Thijs VN, O'Brien MW, et al. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. AJNR Am J Neuroradiol 2001;22:637–644.
20. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(suppl 1):S208–S219.
21. Ghafoorian M, Karssemeijer N, van Uden IW, et al. Automated detection of white matter hyperintensities of all sizes in cerebral small vessel disease. Med Phys 2016;43:6246–6258.
22. van Uden IW, Tuladhar AM, van der Holst HM, et al. Diffusion tensor imaging of the hippocampus predicts the risk of dementia; the RUN DMC study. Hum Brain Mapp 2016;37:327–337.
23. Bowerman BL, O'Connell RT. Linear Statistical Models: An Applied Approach, 2nd ed. Belmont: Duxbury Resource Center; 1990.
24. Schulz UG, Flossmann E, Francis JM, Redgrave JN, Rothwell PM. Evolution of the diffusion-weighted signal and the apparent diffusion coefficient in the late phase after minor stroke: a follow-up study. J Neurol 2007;254:375–383.
25. Garg RK, Liebling SM, Maas MB, Nemeth AJ, Russell EJ, Naidech AM. Blood pressure reduction, decreased diffusion on MRI, and outcomes after intracerebral hemorrhage. Stroke 2012;43:67–71.
26. Menon RS, Burgess RE, Wing JJ, et al. Predictors of highly prevalent brain ischemia in intracerebral hemorrhage. Ann Neurol 2012;71:199–205.
27. Auriel E, Edlow BL, Reijmer YD, et al. Microinfarct disruption of white matter structure: a longitudinal diffusion tensor analysis. Neurology 2014;83:182–188.
28. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. Neurology 2012;79:442–448.
29. van Veluw SJ, Biessels GJ, Klijn CJ, Rozemuller AJ. Heterogeneous histopathology of cortical microbleeds in cerebral amyloid angiopathy. Neurology 2016;86:867–871.
30. van Veluw SJ, Shih AY, Smith EE, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. Lancet Neurol 2017;16:730–740.
31. Ter Telgte A, Wiegertjes K, Tuladhar AM, et al. Investigating the origin and evolution of cerebral small vessel disease: the RUN DMC–InTENse study. ESJ 2018;3:369–378.

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