Cerebral small vessel disease and incident parkinsonism

The RUN DMC study

Helena M. van der Holst, MD
Inge W.M. van Uden, MD
Anil M. Tuladhar, MD
Karlijn F. de Laat, MD, PhD
Anouk G.W. van Norden, MD, PhD
David G. Norris, PhD
Ewoud J. van Dijk, MD, PhD
Rianne A.J. Esselink, MD, PhD
Bram Platel, PhD
Frank-Erik de Leeuw, MD, PhD

Correspondence to Dr. de Leeuw: frankerik.deleeuw@radboudumc.nl

ABSTRACT

Objective: To investigate the relation between baseline cerebral small vessel disease (SVD) and the risk of incident parkinsonism using different MRI and diffusion tensor imaging (DTI) measures.

Methods: In the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) study, a prospective cohort study, 503 elderly participants with SVD and without parkinsonism were included in 2006. During follow-up (2011–2012), parkinsonism was diagnosed according to UK Brain Bank criteria. Cox regression analysis was used to investigate the association between baseline imaging measures and incident all-cause parkinsonism and vascular parkinsonism (VP). Tract-based spatial statistics analysis was used to identify differences in baseline DTI measures of white matter (WM) tracts between participants with VP and without parkinsonism.

Results: Follow-up was available from 501 participants (mean age 65.6 years; mean follow-up duration 5.2 years). Parkinsonism developed in 20 participants; 15 were diagnosed with VP. The 5-year risk of (any) parkinsonism was increased for those with a high white matter hyperintensity (WMH) volume (hazard ratio [HR] 1.8 per SD increase, 95% confidence interval [CI] 1.3–2.4) and a high number of lacunes (HR 1.4 per number increase, 95% CI 1.1–1.8) at baseline. For VP, this risk was also increased by the presence of microbleeds (HR 5.7, 95% CI 1.9–16.8) and a low gray matter volume (HR 0.4 per SD increase, 95% CI 0.2–0.8). Lower fractional anisotropy values in bifrontal WM tracts involved in movement control were observed in participants with VP compared to participants without parkinsonism.

Conclusions: SVD at baseline, especially a high WMH volume and a high number of lacunes, is associated with incident parkinsonism. Our findings favor a role of SVD in the etiology of parkinsonism. *Neurology*® 2015;85:1569–1577

GLOSSARY

CI = confidence interval; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **GM** = gray matter; **HR** = hazard ratio; **IPD** = idiopathic Parkinson disease; **MD** = mean diffusivity; **MMSE** = Mini-Mental State Examination; **PSP** = progressive supranuclear palsy; **RUN DMC** = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort; **SPM** = Statistical Parametric Mapping; **STRIVE** = Standards for Reporting Vascular Changes on Neuroimaging; **SVD** = small vessel disease; **TBSS** = tract-based spatial statistics; **UPDRS-m** = motor part of the Unified Parkinson's Disease Rating Scale; **VP** = vascular parkinsonism; **WM** = white matter; **WMH** = white matter hyperintensity.

Cerebral small vessel disease (SVD) is a frequent finding on brain imaging of the elderly population[1] and has been identified as a cause of motor impairment[2] and gait and balance decline over time.[3] SVD has also been related to parkinsonism, with evidence coming from cross-sectional autopsy studies that found pathologic proof of SVD in patients with parkinsonism, who did not exhibit evidence of histopathologic findings compatible with parkinsonism, including Lewy bodies or tau inclusions.[4,5] Whether parkinsonism is a direct consequence of SVD or a coincidental finding is unknown.

The imaging spectrum of SVD is rapidly expanding from lesions visible on conventional MRI, including white matter hyperintensities (WMHs), lacunes, microbleeds, and (sub)cortical

Editorial, page 1532

Supplemental data at Neurology.org

From the Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Center for Neuroscience, Department of Neurology (H.M.v.d.H., I.W.M.v.U., A.M.T., E.J.v.D., R.A.J.E., F.-E.d.L.), and Radboud University, Donders Institute for Brain, Cognition and Behaviour, Center for Cognitive Neuroimaging (A.M.T., D.G.N.), Nijmegen, the Netherlands; Department of Neurology (K.F.d.L.), HagaZiekenhuis Den Haag, the Netherlands; Department of Neurology (A.G.W.v.N.), Amphia Ziekenhuis Breda, the Netherlands; Erwin L. Hahn Institute for Magnetic Resonance Imaging (D.G.N.), UNESCO-Weltkulturerbe Zollverein, Leitstand Kokerei Zollverein, Essen, Germany; MIRA Institute for Biomedical Technology and Technical Medicine (D.G.N.), University of Twente, Enschede, the Netherlands; and Department of Radiology and Nuclear Medicine (B.P.), Radboud University Medical Center, Nijmegen, the Netherlands.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

atrophy,[6] to changes in diffusion measures of the white matter (WM) assessed by diffusion tensor imaging (DTI),[7] which is regarded as an index of WM structural integrity. Recent cross-sectional DTI studies have shown a relation between diffusion abnormalities in the WM and parkinsonism[8,9]; however, longitudinal studies investigating the role of these MRI and DTI characteristics in the development of parkinsonism are currently lacking. We therefore prospectively investigated the relation between SVD, using baseline MRI and DTI measures, including tract-based spatial statistics (TBSS), and the development of parkinsonism, in order to gain insight into the role of SVD in incident parkinsonism.

METHODS

Study population. This study is embedded in the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) study, a prospective cohort study that investigates the risk factors and clinical consequences of functional and structural brain changes as assessed by MRI in 503 independently living elderly participants with SVD. The primary outcome of the longitudinal part of the RUN DMC study is incident parkinsonism and dementia. The recruitment, study rationale, and protocol of the RUN DMC study have been described in detail elsewhere.[10] SVD was defined as the presence of any WMH or lacunes of presumed vascular origin on brain imaging,[11] because the onset of SVD is often insidious and clinically heterogeneous with acute symptoms (TIAs or lacunar syndromes), or subacute symptoms, including cognitive, motor, or mood disturbances.[12] All consecutive patients referred to our department who underwent diagnostic brain imaging (CT or MRI scan) for several reasons (e.g., stroke, TIA, cognitive complaints) were selected for participation. Inclusion criteria were age between 50 and 85 years and SVD on brain imaging. Main exclusion criteria were parkinsonism, dementia, SVD mimics, and MRI contraindications. Patients eligible because of a lacunar syndrome were included >6 months after the event.

Baseline assessment, including an extensive cognitive and motor evaluation and a cerebral MRI, took place in 2006 among 503 participants. In 2011–2012, this assessment was repeated; 2 participants were lost to follow-up (but not deceased), 49 had died, and 54 refused an in-person follow-up, but their clinical endpoints were available; 398 participated in the follow-up examination (figure e-1 on the *Neurology*® Web site at Neurology.org).

Standard protocol approvals, registrations, and patient consents. All participants signed an informed consent form. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Screening for parkinsonism. A flowchart of the parkinsonism screening is shown in figure 1. The presence of parkinsonian signs was evaluated during an in-person follow-up assessment (n = 398) by 2 trained residents in neurology by using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-m, 27 items, score 0–108).[13] Parkinsonism was defined as the presence of bradykinesia and at least one of the 3 following signs: tremor, rigidity, or gait and postural instability, according to the UK Parkinson's Disease Society Brain Bank criteria.[14] We screened the presence of these 4 signs on the basis of previously established parkinsonian sign scores derived from the UPDRS-m,[15] including limb bradykinesia (based on 8 items: right and left finger taps, handgrip, hand pronation-supination, and leg agility), rigidity (based on 5 items: rigidity of neck and the 4 extremities), tremor (based on 7 items: rest tremor of lip/chin and 4 extremities and action tremor of both arms), and parkinsonian gait (based on 5 items: arise from chair, posture, gait, postural stability, and body bradykinesia). We considered bradykinesia as present when ≥1 items on limb bradykinesia had a score of ≥2,[13,16] to guarantee a high sensitivity of this main symptom of parkinsonism. The other 3 signs (tremor, rigidity, and gait and postural instability) were considered present when the participant had either ≥2 items with a score of ≥1 or 1 item with a score of ≥2 in that specific category.

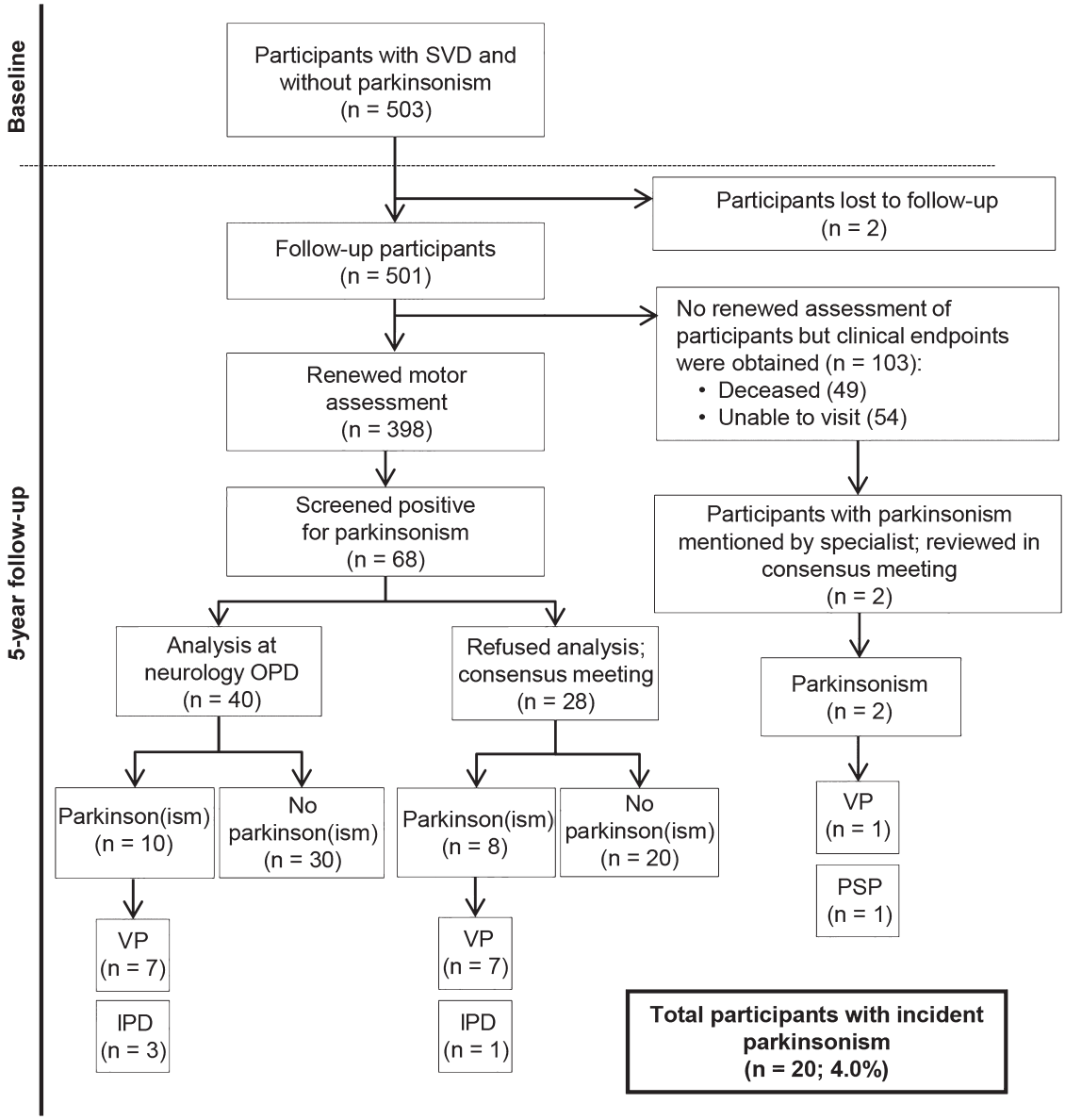
Participants were considered screen-positive when (1) they were already diagnosed with parkinsonism by a neurologist after baseline assessment or (2) they had bradykinesia and one or more of the other 3 signs,[17] according to abovementioned criteria, or (3) had UPDRS-m score ≥10, but did not meet the criteria mentioned in (1) or (2). We added this last criterion because other comorbidities (e.g., stroke, severe polyneuropathy, or rheumatic disease) often influence UPDRS-m scores, which could hinder the evaluation of the presence of parkinsonism.

Of the 398 participants, 68 were considered screen-positive and 40 of them were subsequently examined by a neurologist specialized in movement disorders (R.A.J.E.) for the presence of parkinsonism (10 were diagnosed with parkinsonism; 30 were not). The remaining 28 participants refused this additional evaluation, and for them a consensus diagnosis of parkinsonism was made by a panel, consisting of 2 neurologists, one of whom was specialized in movement disorders (R.A.J.E.). They reviewed all available information on motor performance and imaging, including (1) UPDRS-m scores at baseline and follow-up assessment; (2) information from follow-up neurologic examination, including muscle strength, gait, upper motor neuron signs, sensory deficits, and (primitive) reflexes; (3) medical history; (4) medication; (5) follow-up MRI scan, or if not available, baseline imaging (n = 12); and (6) if applicable, information on the presence of parkinsonism from their treating neurologist. Of these 28 participants, 8 were diagnosed with parkinsonism.

For the participants who did not participate in person (49 deceased and 54 not able to visit our research center), medical records were reviewed and their treating physician was contacted for information on the presence of parkinsonism. In 2 participants, the diagnosis of parkinsonism was reported; after review by the panel, these diagnoses were confirmed, yielding a total of 20 participants with incident parkinsonism.

Parkinsonism was diagnosed based on UK Parkinson's Disease Society Brain Bank criteria for idiopathic Parkinson disease (IPD),[14] Zijlmans et al.[5] criteria for vascular parkinsonism (VP), and National Institute of Neurological Disorders and Stroke–Society for Progressive Supranuclear Palsy criteria for progressive supranuclear palsy (PSP).[14] VP requires the presence of relevant cerebrovascular disease on neuroimaging, operationalized in our study as WMHs beginning to become confluent (Fazekas score ≥2),[18] or the presence of lacunes in basal ganglia or thalamus.[5] Participants with drug-induced parkinsonism were excluded (n = 1). The age at onset of parkinsonism was defined as the midpoint between the date on which parkinsonism was first identified and baseline RUN DMC assessment,[19] or if applicable the date at which participants were last reviewed by a neurologist without notification of hypokinetic-rigid symptoms in-between baseline and follow-up assessment.

Figure 1 Flowchart of parkinsonism case-finding during follow-up



IPD = idiopathic Parkinson disease; OPD = outpatient department; PSP = progressive supranuclear palsy; SVD = cerebral small vessel disease; VP = vascular parkinsonism.

MRI scanning and processing. Baseline MRI was performed on a single 1.5T Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), and included a 3D T1 magnetization-prepared rapid gradient echo, fluid-attenuated inversion recovery (FLAIR), gradient-echo T2*-weighted sequence and a DTI sequence. Details have been described in detail elsewhere.[10]

WMHs were manually segmented on the FLAIR images, with a good interrater variability (intraclass correlation coefficient 0.99). The ratings of lacunes and microbleeds were revised according to the recently published Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)[6] by trained raters blinded to clinical information. The intrarater and interrater variability in a random sample of 10% was good, with weighted kappa of 0.87 and 0.95, respectively, for presence of lacunes, and 0.85 and 0.86 for presence of microbleeds. Automated segmentation on T1 images was performed using Statistical Parametric Mapping (SPM5), to obtain gray matter (GM), WM, and CSF probability maps. These maps were binarized by applying a 0.5 threshold and summed to supply total volumes. All volumes were normalized to the total intracranial volume to adjust for head size.[20] The DTI analysis has been described in detail elsewhere.[10] For TBSS analysis, DTIFit within the FSL toolbox was used to generate fractional anisotropy (FA) and mean diffusivity (MD) images, which were imported into the TBSS pipeline.[21] To create a FA skeleton, the mean FA image was thinned and subsequently this skeleton was thresholded at 0.3 to include major WM tracts. Of the 501 participants (2 were lost to follow-up), 4 were excluded from TBSS analysis because of imaging artefacts, 54 because of territorial infarcts, 2 because of missing values of microbleeds, and 5 because of parkinsonism other than VP, yielding a subgroup of 436 participants (9 with VP and 427 without parkinsonism).

Other measurements. We used the Mini-Mental State Examination (MMSE) score to indicate global cognitive status.

Statistical analysis. Statistical analyses were performed using IBM (Armonk, NY) SPSS Statistics 20. The person-years at risk for each participant were defined as the time between baseline assessment and onset of parkinsonism, date of follow-up assessment, or death, depending on which event occurred first. Cumulative risk of (any) parkinsonism and separate for VP, being the largest group in our study, was estimated with a Kaplan-Meier analysis. Differences in baseline characteristics between participants with VP or IPD/PSP and without parkinsonism were tested by univariate analyses, using an independent samples t test, χ^2 test, Fisher exact test, or Mann-Whitney U test, when appropriate (table 1).

Cox regression analysis was used to calculate hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) of baseline imaging characteristics for (any) parkinsonism and VP separately. Adjustments were made for baseline age, sex, UPDRS-m score, territorial infarcts, and for GM volume or 4 SVD characteristics (WMH volume, WM volume, number of lacunes, and microbleeds). Verification of proportionality of hazards was performed by examining Schoenfeld residuals. Bonferroni corrections were used to correct for multiple comparisons; p values ≤ 0.00714 were considered significant.

To compare voxel-wise analyses of DTI measures between those with VP and without parkinsonism, a 2-sample t test was performed, using a permutation-based statistical interference as part of FSL toolbox (randomise), with a standard number of permutation tests set at 5,000. To identify significant associations, a threshold-free cluster enhancement with a p value <0.025, corrected for multiple comparisons, was used.

RESULTS The total study population consisted of 501 participants; 2 were lost to follow-up. Mean follow-up duration was 5.2 years (SD 0.7). Parkinsonism developed in 20 participants (4.0%); 15 were diagnosed with VP, with all patients having predominantly lower body symptoms and a bilateral onset, 4 with IPD, and 1 with PSP. The cumulative 5-year risk of (any) parkinsonism was 3.5% (95% CI 1.9–5.2) and of VP 2.9% (95% CI 1.4–4.4). One participant with VP was excluded because of baseline T1/T2 artefacts.

Table 1 shows the baseline characteristics of the total study population, and for participants with VP, IPD/PSP, and without parkinsonism separately. The mean baseline age of the total population was 65.6 years (SD 8.8); 56.8% were men. Participants with VP, in comparison to participants without parkinsonism, were older ($p = 0.009$), had a lower MMSE score ($p = 0.039$), and had a higher UPDRS-m score ($p = 0.001$) at baseline. Furthermore, all baseline

Table 1 Baseline characteristics of the total study population and of participants with VP, with IPD/PSP, and without parkinsonism

	Total, n = 500	VP, n = 14	IPD/PSP, n = 5	No parkinsonism, n = 481
Baseline demographics				
Age at baseline, y, mean ± SD	65.6 ± 8.8	70.7 ± 6.3	68.7 ± 8.1	65.5 ± 8.8
Male, n (%)	284 (56.8)	9 (64.3)	4 (80.0)	271 (56.3)
MMSE at baseline, mean ± SD	28.1 ± 1.6	27.4 ± 1.4	27.0 ± 1.9	28.2 ± 1.6
UPDRS-m total score at baseline, median (IQR)	0.0 (0.0; 1.0)[a]	2.0 (0.0; 6.0)	3.0 (2.0; 4.0)[a]	0.0 (0.0; 1.0)
Baseline MRI measures				
WMH volume, mL, median (IQR)	7.2 (3.6; 18.4)	30.0 (16.6; 56.9)	5.4 (3.7; 22.1)	7.0 (3.4; 17.7)
Lacunes, n (%)	134 (26.8)	11 (78.6)	2 (40.0)	121 (25.2)
Microbleeds, n (%)	80 (16.0)[b]	8 (57.1)	0 (0.0)	72 (15.0)[b]
White matter volume, mL, mean ± SD	464.7 ± 51.9	422.9 ± 63.4	452.9 ± 33.8	466.1 ± 51.2
Gray matter volume, mL, mean ± SD	630.9 ± 53.9	580.0 ± 48.2	634.5 ± 76.7	632.3 ± 53.2
Territorial infarcts, n (%)	56 (11.2)	5 (35.7)	1 (20.0)	50 (10.4)
Baseline DTI measures, mean ± SD	n = 497[c]	n = 14	n = 5	n = 478[c]
White matter global FA	0.33 ± 0.02	0.31 ± 0.03	0.34 ± 0.02	0.33 ± 0.02
WMH global FA	0.34 ± 0.03	0.31 ± 0.03	0.35 ± 0.03	0.34 ± 0.03
NAWM global FA	0.33 ± 0.02	0.31 ± 0.03	0.34 ± 0.02	0.33 ± 0.02
White matter global MD	0.89 ± 0.05	0.95 ± 0.05	0.87 ± 0.04	0.89 ± 0.04
WMH global MD	1.00 ± 0.07	1.09 ± 0.06	0.99 ± 0.07	1.00 ± 0.07
NAWM global MD	0.89 ± 0.04	0.94 ± 0.04	0.87 ± 0.03	0.89 ± 0.04

Abbreviations: DTI = diffusion tensor imaging; FA = fractional anisotropy; IPD = idiopathic Parkinson disease; IQR = interquartile range; MD = mean diffusivity ($*10^{-3}$ mm^2/s); MMSE = Mini-Mental State Examination; NAWM = normal-appearing white matter; PSP = progressive supranuclear palsy; UPDRS-m = Unified Parkinson's Disease Rating Scale motor score; VP = vascular parkinsonism; WMH = white matter hyperintensities.
Brain volumes are represented normalized to the total intracranial volume.
[a] One participant was excluded because of missing values of UPDRS-m at baseline.
[b] Four participants were excluded because of missing values of microbleeds at baseline.
[c] Three participants were excluded because of baseline DTI artefacts.

imaging characteristics shown in table 1 differed significantly ($p < 0.05$) between those groups.

One participant with IPD was excluded because of a missing baseline UPDRS-m score.

There was a strong relation between WMH volume and the number of lacunes and the 5-year risk of (any) parkinsonism (table 2). The 5-year risk of VP was increased for those with a high WMH volume (HR 2.0 per SD increase [mL]; 95% CI 1.4–2.7), a high number of lacunes (HR 1.5 per number increase; 95% CI 1.2–1.9), presence of microbleeds (HR 5.7; 95% CI 1.9–16.8), and a low GM volume (HR 0.4 per SD increase [mL]; 95% CI 0.2–0.8) (table 3).

A TBSS analysis showed differences in baseline DTI values between participants with VP and those without parkinsonism (figure 2). Lower FA values were seen in WM tracts in the bilateral frontal and right parietal lobe—genu of corpus callosum, internal capsule, superior longitudinal fasciculus, forceps minor, inferior fronto-occipital fasciculus, cingulum bundle, superior and posterior (right) corona radiate, and right posterior thalamic radiation—in participants with VP, even after adjustment for different SVD characteristics. In addition, higher MD values were seen in VP patients in a similar pattern, although most voxels lost signal after adjustment for SVD, except in the anterior corona radiata (data not shown).

DISCUSSION This is a unique prospective study investigating the relation between cerebral SVD at baseline and the risk of incident parkinsonism. We showed that a high WMH volume and a high number of lacunes were associated with an increased 5-year risk of (any) parkinsonism. For VP, this risk was also increased by the presence of microbleeds and a low GM volume. Furthermore, we observed lower FA values especially in bifrontal WM tracts involved in movement control in participants with

Table 2 Relation between baseline MRI and DTI measures and the risk of (any) parkinsonism at follow-up

	Hazard ratio (95% CI), adjusted for baseline age, sex, baseline UPDRS-m score, and territorial infarcts	*p* Value	Hazard ratio (95% CI), in addition adjusted for gray matter volume[a] or SVD characteristics[b]	*p* Value
Baseline MRI measures (n = 499)[c]				
WMH volume, per SD (mL)	1.74 (1.33–2.27)	<0.001[d]	1.75 (1.31–2.35)[a]	<0.001[d]
Lacunes, presence	4.74 (1.55–14.51)	0.006[d]	3.66 (1.19–11.32)[a]	0.024
Lacunes, per number	1.52 (1.21–1.91)	<0.001[d]	1.43 (1.13–1.80)[a]	0.003[d]
Microbleeds, presence[e]	3.87 (1.50–10.01)	0.005[d]	3.52 (1.36–9.09)[a]	0.009
Microbleeds, per number[e]	1.07 (0.98–1.17)	0.144	1.09 (0.99–1.19)[a]	0.087
White matter volume, per SD (mL)	0.73 (0.41–1.28)	0.267	0.64 (0.34–1.18)[a]	0.151
Gray matter volume, per SD (mL)	0.42 (0.23–0.76)	0.004[d]	0.48 (0.27–0.87)[b]	0.016
	Hazard ratio (95% CI), adjusted for baseline age, sex, baseline UPDRS-m score, and territorial infarcts	***p* Value**	**Hazard ratio (95% CI), in addition adjusted for gray matter volume[a] and SVD characteristics[b]**	***p* Value**
Baseline DTI measures, (n = 496)[f]				
White matter global FA, per SD	0.76 (0.47–1.24)	0.275	1.40 (0.80–2.44)[a,b]	0.244
WMH global FA, per SD	0.54 (0.30–0.97)	0.038	0.90 (0.49–1.66)[a,b]	0.729
NAWM global FA, per SD	0.77 (0.47–1.26)	0.300	1.42 (0.81–2.49)[a,b]	0.225
White matter global MD, per SD	1.70 (0.99–2.90)	0.053	0.71 (0.36–1.42)[a,b]	0.333
WMH global MD, per SD	2.49 (1.45–4.28)	0.001[d]	1.39 (0.4–3.01)[a,b]	0.401
NAWM global MD, per SD	1.48 (0.85–2.58)	0.165	0.66 (0.35–1.27)[a,b]	0.218

Abbreviations: CI = confidence interval; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity (*10^{-4} mm^2/s); NAWM = normal-appearing white matter; per SD = hazard ratios per SD difference from the mean; SVD = small vessel disease; UPDRS-m = Unified Parkinson's Disease Rating Scale motor score; WMH = white matter hyperintensities.

[a] In addition adjusted for gray matter volume.

[b] In addition adjusted for SVD characteristics: including white matter volume, WMH volume, number of lacunes and microbleeds.

[c] One participant with idiopathic Parkinson disease was excluded in addition because baseline UPDRS-m score was missing.

[d] Significant after Bonferroni correction.

[e] Four participants were excluded because of missing values of microbleeds at baseline.

[f] Three participants were excluded in addition because of baseline DTI artefacts.

Table 3 Relation between baseline MRI and DTI measures and the risk of vascular parkinsonism at follow-up

	Hazard ratio (95% CI), adjusted for baseline age, sex, baseline UPDRS-m score, and territorial infarcts	*p* Value	Hazard ratio (95% CI), in addition adjusted for gray matter volume[a] or SVD characteristics[b]	*p* Value
Baseline MRI measures (n = 495)[c]				
WMH volume, per SD (mL)	1.92 (1.45–2.55)	<0.001[d]	1.99 (1.44–2.73)[a]	<0.001[d]
Lacunes, presence	6.60 (1.68–25.89)	0.007[d]	4.68 (1.18–18.56)[a]	0.028
Lacunes, per number	1.61 (1.26–2.05)	<0.001[d]	1.49 (1.16–1.92)[a]	0.002[d]
Microbleeds, presence[e]	6.52 (2.21–19.22)	0.001[d]	5.68 (1.92–16.84)[a]	0.002[d]
Microbleeds, per number[e]	1.08 (0.99–1.18)	0.083	1.10 (1.01–1.21)[a]	0.035
White matter volume, per SD (mL)	0.64 (0.33–1.23)	0.177	0.51 (0.24–1.07)[a]	0.073
Gray matter volume, per SD (mL)	0.32 (0.16–0.64)	0.001[d]	0.39 (0.19–0.77)[b]	0.007[d]
	Hazard ratio (95% CI), adjusted for baseline age, sex, baseline UPDRS-m score, and territorial infarcts	***p* Value**	**Hazard ratio (95% CI), in addition adjusted for gray matter volume[a] and SVD characteristics[b]**	***p* Value**
Baseline DTI measures (n = 492)[f]				
White matter global FA, per SD	0.52 (0.30–0.89)	0.017	1.12 (0.59–2.11)[a,b]	0.729
WMH global FA, per SD	0.39 (0.19–0.77)	0.007[d]	0.87 (0.42–1.78)[a,b]	0.693
NAWM global FA, per SD	0.53 (0.31–0.91)	0.022	1.14 (0.60–2.17)[a,b]	0.681
White matter global MD, per SD	2.49 (1.40–4.43)	0.002[d]	0.83 (0.39–1.80)[a,b]	0.645
WMH global MD, per SD	3.77 (2.02–7.04)	<0.001[d]	1.81 (0.72–4.56)[a,b]	0.211
NAWM global MD, per SD	2.20 (1.19–4.06)	0.012	0.79 (0.38–1.62)[a,b]	0.514

Abbreviations: CI = confidence interval; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity (*10^{-4} mm^2/s); NAWM = normal-appearing white matter; per SD = hazard ratios per SD difference from the mean; SVD = small vessel disease; UPDRS-m = Unified Parkinson's Disease Rating Scale motor score; WMH = white matter hyperintensities.

[a] In addition adjusted for gray matter volume.

[b] In addition adjusted for SVD characteristics: including white matter volume, WMH volume, number of lacunes and microbleeds.

[c] Five participants were excluded because of a diagnosis of parkinsonism other than vascular parkinsonism.

[d] Significant after Bonferroni correction.

[e] Four participants were excluded because of missing values of microbleeds at baseline.

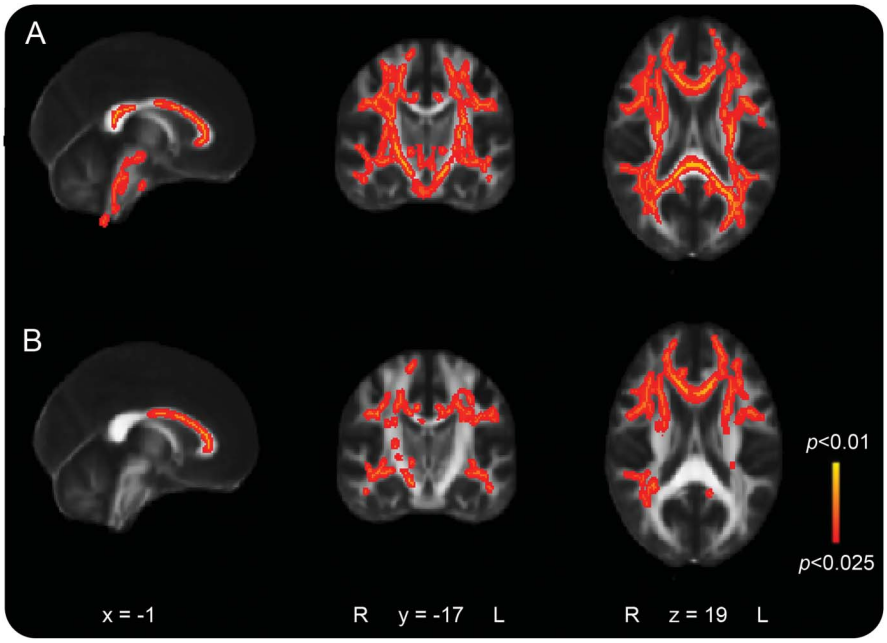
[f] Three participants were excluded in addition because of baseline DTI artefacts.

VP compared to participants without parkinsonism, independent of SVD.

Major strengths of our study are its longitudinal and single-center design, which allowed us to use identical motor and cognitive assessments during baseline and follow-up. Furthermore, the large sample size and high follow-up rate of 99.6% are main advantages. Moreover, all imaging data were analyzed by raters blinded to clinical information with a good intrarater and interrater variability. Finally, we were able to make appropriate adjustments, reducing the risk of confounding. We intentionally did not adjust for vascular risk factors as we considered them part of the causal chain between SVD and parkinsonism.

Several methodologic issues need to be addressed. First, because of the small number of patients with parkinsonism in our study, our results should be interpreted with caution. Second, we were not able to diagnose parkinsonism in the same way for all patients. For participants who were not able to participate in person, we had to rely on information from medical files and we could have missed the diagnosis of parkinsonism in some, since parkinsonism is frequently accepted as part of normal aging. Some participants who participated in person and were considered screen-positive for the presence of parkinsonian signs refused additional evaluation by a neurologist specialized in movement disorders (28 of 68 participants). However, all 28 participants were examined in the follow-up assessment by 2 skilled neurologists in training with extensive experience in diagnosing parkinsonism, after which a consensus diagnosis was made by an expert panel. The similarity of the diagnostic approaches is well-illustrated by a virtual identical proportion of the patients with parkinsonism identified by the 2 approaches. Third, misclassification could have occurred as the accuracy of clinical diagnosis of the different etiologies underlying parkinsonism, compared to neuropathologic diagnosis, is relatively low.[22] We therefore initially classified any parkinsonism;

Figure 2 Differences in fractional anisotropy values between participants with vascular parkinsonism and without parkinsonism



Voxel-wise analysis of the differences in fractional anisotropy (FA) values between participants with vascular parkinsonism (n = 9) and without parkinsonism (n = 427). Adjusted for age, sex, baseline motor part of the Unified Parkinson's Disease Rating Scale score, and normalized total brain volume (A) and for small vessel disease characteristics (white matter volume, white matter hyperintensity volume, and number of lacunes and microbleeds) (B), performed with a 2-sample t test, thresholded at $p < 0.025$ and corrected for multiple comparisons. These images are superimposed onto the spatially normalized Montreal Neurological Institute (MNI) stereotactic space FA map. The x, y, and z coordinates represent the MNI coordinates of each slide.

thereafter, neuroimaging was used to allow for the diagnosis of VP. Fourth, as imaging information is needed to classify the different etiologies of parkinsonism, especially concerning VP, circular reasoning might have occurred in our analyses with VP, although we used baseline MRI and DTI measures, when all participants were free of parkinsonism.

Even though this is a hospital-based cohort study, our results have a high external validity for an elderly population with SVD who visit a general neurology department, as we included all consecutive patients with SVD on neuroimaging (CT or MRI scan) performed because of major referral reasons (e.g., TIA, stroke, cognitive complaints) and there were no restrictions for admission to our hospital.

So far, the exact role of SVD in parkinsonism is unknown. Some studies have suggested that WMHs are more common in patients with parkinsonism,[23,24] whereas others failed to demonstrate that.[25,26] Furthermore, in autopsy studies, only a small subset (<10%) of parkinsonism was attributed to vascular lesions, because of the absence of other pathologic findings (Lewy bodies or tau inclusions) compatible with a known parkinsonian syndrome.[22]

Our findings favor a role for SVD in the development of parkinsonism, as we showed that participants with a high degree of SVD had an increased risk of incident parkinsonism. Furthermore, we found a relatively high incidence of parkinsonism compared to population-based studies; in the Rotterdam Study, 2% of the 6,566 participants (≥55 years) developed (any) parkinsonism after a mean follow-up duration of 5.8 years,[19] vs 4% in our study, which may also indicate that SVD contributes to the etiology of parkinsonism.

DTI has gained increased interest in the diagnostic process of parkinsonism in recent years,[8] as it has been suggested that this technique could be of help in differentiating among the different subtypes of parkinsonism.[27,28] We therefore performed a TBSS analysis in patients with a clinical diagnosis of VP, because this was the largest group of patients in our study and a recent study showed that DTI can differentiate between VP and parkinsonian syndromes of degenerative origin.[28] We found lower FA values in bilateral WM tracts involved in movement control in VP compared to participants without parkinsonism, even after adjustment for SVD characteristics. This result is in line with a recent cross-sectional DTI study in patients with VP and healthy controls; however, no adjustments were made for SVD.[9] Using DTI measures of scans at a point in time when all participants

were free of parkinsonism is unique in our study. Our results may suggest that diffusion changes can be an early marker of VP. However, a note of caution is due here owing to the small number of patients with VP in our study.

We can hypothesize about the role of SVD in parkinsonism; it may be that SVD disrupts the structural integrity of WM tracts, including disruption of the thalamocortical fibers, thereby reducing the influence of the basal ganglia on motor, premotor, and supplementary motor cortices.[29] Disconnection of the basal ganglia–thalamocortical circuit possibly leads to (sub) cortical atrophy, ultimately resulting in parkinsonism. Furthermore, SVD could possibly lower the threshold for developing parkinsonism, by lowering the threshold for Lewy body pathology to become symptomatic, for example. In addition, marked loss of striatal dopaminergic innervations that occurs during aging might contribute as well.[30]

Future studies are needed to further investigate the contribution of SVD to incident parkinsonism, ideally taking into account the changes in these imaging markers over time.

AUTHOR CONTRIBUTIONS

All authors agreed to the conditions noted on the Authorship Agreement From. Dr. van der Holst: involved in data collection, analysis and interpretation of data, and drafting and revising the manuscript. Dr. van Uden: involved in data collection and revising the manuscript. Dr. Tuladhar: involved in data collection, data analysis, and revising the manuscript. Dr. de Laat: involved in study concept and design, data collection, and revising the manuscript. Dr. van Norden: involved in study concept and design, data collection, and revising the manuscript. Prof. Norris: involved in study concept and design and revising the manuscript. Dr. van Dijk: involved in study concept and design and revising the manuscript. Dr. Esselink: involved in data collection and revising the manuscript. Dr. Platel: involved in imaging analysis and revising the manuscript. Dr. de Leeuw: involved in study concept and design, analysis and interpretation of data, revising the manuscript, study supervision, and obtaining funding.

STUDY FUNDING

Supported by the "Dutch Brain Foundation" and by the "Netherlands Organization for Scientific Research."

DISCLOSURE

H. van der Holst, I. van Uden, A. Tuladhar, K. de Laat, A. van Norden, and D. Norris report no disclosures relevant to the manuscript. E. van Dijk received a personal fellowship from the Dutch Brain Foundation (H04-12; F2009[1]-16). R. Esselink and B. Platel report no disclosures relevant to the manuscript. F. de Leeuw received a personal fellowship from the Dutch Brain Foundation (H04-12; F2009[1]-16) and a VIDI innovational grant from the Netherlands Organization for Scientific Research (grant number 016.126.351). Go to Neurology.org for full disclosures.

Received February 16, 2015. Accepted in final form June 12, 2015.

REFERENCES

1. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study: The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70:9–14.
2. Baezner H, Blahak C, Poggesi A, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology 2008;70:935–942.
3. Kreisel SH, Blahak C, Bazner H, et al. Deterioration of gait and balance over time: the effects of age-related white matter change: the LADIS study. Cerebrovasc Dis 2013;35:544–553.
4. Yamanouchi H, Nagura H. Neurological signs and frontal white matter lesions in vascular parkinsonism: a clinicopathologic study. Stroke 1997;28:965–969.
5. Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ. Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. Mov Disord 2004;19:630–640.
6. 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.
7. de Groot M, Verhaaren BF, de Boer R, et al. Changes in normal-appearing white matter precede development of white matter lesions. Stroke 2013;44:1037–1042.
8. Cochrane CJ, Ebmeier KP. Diffusion tensor imaging in parkinsonian syndromes: a systematic review and meta-analysis. Neurology 2013;80:857–864.
9. Wang HC, Hsu JL, Leemans A. Diffusion tensor imaging of vascular parkinsonism: structural changes in cerebral white matter and the association with clinical severity. Arch Neurol 2012;69:1340–1348.
10. 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.
11. Erkinjuntti T. Subcortical vascular dementia. Cerebrovasc Dis 2002;2:58–60.
12. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426–436.
13. Fahn S, MC, Calne D, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NJ: MacMillan Healthcare Information; 1987.
14. Litvan I, Bhatia KP, Burn DJ, et al. Movement disorders society scientific issues committee report: SIC task force appraisal of clinical diagnostic criteria for parkinsonian disorders. Mov Disord 2003;18:467–486.
15. Buchman AS, Shulman JM, Nag S, et al. Nigral pathology and parkinsonian signs in elders without Parkinson disease. Ann Neurol 2012;71:258–266.
16. Louis ED, Luchsinger JA. History of vascular disease and mild parkinsonian signs in community-dwelling elderly individuals. Arch Neurol 2006;63:717–722.
17. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351–356.
19. de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. Neurology 2004;63:1240–1244.

20. Colliot O, Chetelat G, Chupin M, et al. Discrimination between Alzheimer disease, mild cognitive impairment, and normal aging by using automated segmentation of the hippocampus. Radiology 2008;248:194–201.
21. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487–1505.
22. Horvath J, Burkhard PR, Bouras C, Kovari E. Etiologies of Parkinsonism in a century-long autopsy-based cohort. Brain Pathol 2013;23:28–33.
23. Stern MB, Braffman BH, Skolnick BE, Hurtig HI, Grossman RI. Magnetic resonance imaging in Parkinson's disease and parkinsonian syndromes. Neurology 1989;39:1524–1526.
24. Piccini P, Pavese N, Canapicchi R, et al. White matter hyperintensities in Parkinson's disease: clinical correlations. Arch Neurol 1995;52:191–194.
25. Schwartz RS, Halliday GM, Cordato DJ, Kril JJ. Small-vessel disease in patients with Parkinson's disease: a clinicopathological study. Mov Disord 2012;27:1506–1512.
26. Dalaker TO, Larsen JP, Bergsland N, et al. Brain atrophy and white matter hyperintensities in early Parkinson's disease. Mov Disord 2009;24:2233–2241.
27. Meijer FJ, Bloem BR, Mahlknecht P, Seppi K, Goraj B. Update on diffusion MRI in Parkinson's disease and atypical parkinsonism. J Neurol Sci 2013;332:21–29.
28. Deverdun J, Menjot de Champfleur S, Cabello-Aguilar S, et al. Diffusion tensor imaging differentiates vascular parkinsonism from parkinsonian syndromes of degenerative origin in elderly subjects. Eur J Radiol 2014;83:2074–2079.
29. Galvan A, Wichmann T. Pathophysiology of parkinsonism. Clin Neurophysiol 2008;119:1459–1474.
30. Umegaki H, Roth GS, Ingram DK. Aging of the striatum: mechanisms and interventions. Age 2008;30:251–261.

Neurology®

Cerebral small vessel disease and incident parkinsonism: The RUN DMC study

Helena M. van der Holst, Inge W.M. van Uden, Anil M. Tuladhar, et al.

Neurology 2015;85;1569-1577 Published Online before print October 7, 2015
DOI 10.1212/WNL.0000000000002082