Diffusion Tensor Imaging and Gait in Elderly Persons With Cerebral Small Vessel Disease

Karlijn F. de Laat, MD; Anouk G.W. van Norden, MD; Rob A.R. Gons, MD; Lucas J.B. van Oudheusden, MD; Inge W.M. van Uden, MD; David G. Norris, PhD; Marcel P. Zwiers, PhD; Frank-Erik de Leeuw, MD, PhD

Background and Purpose—Although cerebral small vessel disease, including white matter lesions (WML) and lacunar infarcts, is associated with gait disturbances, not all individuals with small vessel disease have these disturbances. Identical-appearing WML on MRI could reflect different degrees of microstructural integrity. Moreover, conventional MRI does not assess the integrity of normal-appearing white matter (NAWM). We therefore investigated the relation between white matter integrity assessed by diffusion tensor imaging in WML, NAWM, several regions of interest, and gait.

Methods—A total of 484 nondemented elderly persons between 50 and 85 years old with cerebral small vessel disease were included in this analysis and underwent MRI and diffusion tensor imaging scanning. Mean diffusivity and fractional anisotropy within WML, NAWM, and regions of interest were related to quantitative and semiquantitative gait parameters.

Results—Mean diffusivity in the WML was inversely related with gait (velocity $v$ = $-0.15; P = 0.002$). For the fractional anisotropy, this relation was less evident. The same was found in the NAWM (velocity $v$ = $-0.21; P < 0.001$) and for some parameters also after additional adjustment for WML and lacunar infarcts.

Conclusion—This study indicates that integrity of both WML and NAWM, beyond the detection limit of conventional MRI, is associated with gait disturbances. (Stroke. 2011;42:373-379.)

Key Words: cerebral small vessel disease ▪ diffusion tensor imaging ▪ gait

Cerebral small vessel disease (SVD), including white matter lesions (WML) and lacunar infarcts, is related to gait disturbances,1 an often neglected but nevertheless serious consequence of SVD that is associated with increased morbidity and mortality.2 However, not everyone with SVD has gait disturbances; its prevalence is $\approx35$%,2 which is far less than the 90% prevalence of SVD in elderly persons.3 Although we demonstrated that the different severity of WML and lacunar infarcts could partially account for this discrepancy,1 even subjects with a similar degree of WML may have a different degree of gait impairment.4

Because identical-appearing WML on conventional MRI are actually histopathologically heterogeneous,5 it could be that only WML with the highest loss of microstructural integrity are related to gait disturbances. Moreover, MRI is not sensitive to early loss of microstructural integrity of the normal-appearing white matter (NAWM). Abnormalities in this part of the white matter nevertheless may be presentâ and therefore may contribute to the development of gait disturbances. Because previous studies have demonstrated that WML in the frontal lobe are most related to gait performance,7 the location of damage to the white matter also may be important. However, studies of normal gait have found that networks involved in its control are widespread in the entire brain.8 In addition, conventional MRI parameters other than WML or lacunar infarcts, such as total brain volume (TBV), may play a role in the development of gait disturbances. TBV has been found to be a strong predictor for cognitive dysfunction in subjects with SVD,9 but the association with gait disturbances has only been studied sparsely.10

Diffusion tensor imaging (DTI)11 allows assessment of the microstructural integrity of the whole white matter.12 A reduction in fractional anisotropy (FA) and increase in mean diffusivity (MD) are believed to represent reduced microstructural integrity in SVD.13 Only 2 studies reported on the association between low FA or high MD in the corpus callosum and gait impairment, but they did not investigate or failed to demonstrate an association in the white matter outside the corpus callosum. The aim of this study therefore was to investigate the association between the microstructural...
Subjects and Methods

This study is embedded in the Radboud University Nijmegen Diffusion tensor and MRI Cohort (RUN DMC) study, a prospective cohort study that was designed to investigate risk factors and cognitive, motor, and mood consequences of functional and structural brain changes among elderly persons with cerebral SVD. The primary study outcome of the longitudinal part of the RUN DMC study is the development of dementia or parkinsonism.

Cerebral SVD is characterized on neuroimaging by either WML or lacunar infarcts. Symptoms of SVD include acute symptoms, such as TIA or lacunar syndromes, or subacute manifestations, such as cognitive disturbances, motor (gait) disturbances, and/or depressive symptoms.28 Because the onset of cerebral SVD is often insidious, clinically heterogeneous, and typically with mild symptoms, it has been suggested that the selection of subjects with cerebral SVD in clinical studies should be based on the more consistent brain imaging features.17 Accordingly, in 2006, consecutive patients referred to the Department of Neurology between October 2002 and November 2006 were selected for participation.

Inclusion criteria were age between 50 and 85 years and cerebral SVD on neuroimaging (WML and/or lacunar infarct). Subsequently, the aforementioned acute or subacute clinical symptoms of SVD were assessed by standardized structured assessments (a questionnaire for TIA and stroke;24 the Cognitive Failures Questionnaire, which also includes executive functions, for cognition;19 the Falls Questionnaire23 and the Freezing of Gait Questionnaire for gait;21 and the Center of Epidemiological Studies-Depression scale22 and use of antidepressive medication for depressive symptoms. Patients who were eligible because of a lacunar syndrome were included only >6 months after the event to avoid acute effects on the outcomes.

Exclusion criteria were: (1) dementia;23 (2) parkinsonism;24 (3) intracranial hemorrhage; (4) life expectancy <6 months; (5) intracranial space-occupying lesion; (6) (psychiatric) disease interfering with cognitive testing or follow-up; (7) recent or current use of acetycholine-esterase inhibitors, neuroleptic agents, L-dopa or dopa-agonists or antagonists; (8) non-SVD-related WML (eg, multiple sclerosis); (9) prominent visual or hearing impairment; (10) language barrier; and (11) MRI contraindications or known claustrophobia.

From 1004 individuals invited by letter, 727 were eligible after contact by phone and 525 agreed to participate. In 22 subjects, exclusion criteria were found during their visit to our research center (dementia [n=4], Parkinson’s disease [n=1], current levodopa use [n=1], multiple sclerosis [n=1], language barrier [n=1], death before MRI scanning [n=1], or unexpected claustrophobia [n=14]), yielding a response rate of 71.3% (503/705).

The reasons for referral in this group included those corresponding to symptoms of SVD, eg, TIA/minor stroke and cognitive and motor syndromes. Based on former assessments, these 503 individuals had acute symptoms, such as TIA or lacunar syndrome (n=219), or subacute symptoms, such as cognitive disturbances (n=245), motor disturbances (n=97), depressive symptoms (n=100), or a combination thereof. A motor disturbance was defined in accordance with operationalization as used in other large-scale studies on cerebral SVD and gait20 as follows: a reported history of ≥1 falls during the past year or a self-reported slowing of gait.

All participants signed an informed consent form. The Medical Review Ethics Committee of the region Arnhem-Nijmegen approved the study.

Measurement of Gait

Quantitative gait analysis was performed with a 5.6-m electronic portable walkway (GAITRite; MAP/CIR Inc, Havertown, PA). All subjects walked 2 times at a self-selected normal speed. We measured velocity (m/s), consisting of both the stride length (m; the distance between the heel points of 2 consecutive footprints of the same foot) and cadence (number of steps per minute), stride width (cm; the distance between 1 midpoint of a footprint and the line of progression of the opposite foot), double support percentage (percent of the gait cycle time during which both feet are on the floor), and the variability of stride length, stride time, and stride width. Variability was expressed as coefficients of variation: SD/mean × 100%. Semiqualitative assessment existed of the modified Timetti test with 17 items: 9 for body balance (score, 0–16) and 8 for gait (score, 0–12), with a maximum score of 28, as well as the Timed-Up-and-Go test, which was executed 3 times. Inter-rater reliability was calculated in a random sample of 15% with an intraclass correlation coefficient of 0.99.

MRT Techniques

All MRT scans of all subjects were acquired on a single 1.5-Tesla scanner (Magnetom Sonata; Siemens Medical Solutions). The protocol included a 3-dimensional T1 magnetization-prepared rapid gradient-echo sequence (repetition time/echo time/inversion time, 2250/6.88/850 ms; flip angle, 15°; voxel size, 1.0×1.0×1.0 mm), a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time/echo time/inversion time, 9000/84/2200 ms; voxel size, 1.0×1.2×5.0 mm, plus an interslice gap of 1 mm), and a DTI sequence (repetition time/echo time, 10 100/93 ms, voxel size, 2.5×2.5×2.5 mm, 4 unweighted scans, 30 diffusion-weighted scans with b-value of 900 s/mm²). During the study period, there were no changes in scanner hardware or software or in the scanning protocol.

Magnetization-Prepared Rapid Gradient-Echo and FLAIR Analyses

White matter signal hyperintensities in both supratentorial and infratentorial regions on FLAIR scans, which were not or only faintly hypointense on T1-weighted images, were considered WML, except for gliosis surrounding infarcts. WML were manually segmented on the FLAIR images by 2 trained raters. Total WML volume was calculated by summing the segmented areas multiplied by slice thickness. Lacunar infarcts were rated and defined as areas with diameters of >2 mm and <15 mm with low signal intensity on T1 and FLAIR, ruling out enlarged perivascular spaces and infratemporal pseudolacunes.26 All imaging analyses were performed by raters blinded to clinical information. In a random sample of 10%, inter-rater variability for total WML volume yielded an intraclass correlation coefficient of 0.99; intrarater and inter-rater reliability for the number of lacunar infarcts yielded weighted kappa scores of 0.80 and 0.88.

Automated segmentation on the T1 images was conducted using Statistical Parametric Mapping (SPM5; http://www.fil.ion.ucl.ac.uk/spm/) to obtain gray and white matter and cerebrospinal fluid probability maps.22 These maps were thresholded at 0.5 to provide total volumes. TBV was calculated as the sum of total gray and white matter volumes. Mutual information coregistration (SPM5) was used to align WML maps to the T1 image and to yield a NAWM map (the complement of WML in white matter).

DTI Analysis

The diffusion-weighted images of each subject were realigned on the mean of the realigned weighted images using the mutual information coregistration routines (SPM5). The diffusion tensor11 and its Eigen values were computed using a SPM5 add-on (http://sourceforge.net/projects/spmtools). Spurious negative Eigen values were set to 0, after which the FA and MD were calculated.28 The mean unweighted image was used to compute the coregistration parameters to the T1 image, which were then applied to all diffusion-weighted images and results. All images were visually checked for motion artifacts and coregistration errors.

The volume-averaged FA and MD were calculated in the WML, NAWM, and ROI. ROI were spherical (diameter, 10 mm) and placed...
on 3 axial slices of the Montreal Neurological Institute T1 (MNI152) template (Figure 1). Two slices including the anterior horns (frontal lobe) and posterior horns (temporal/occipital lobes) of the lateral ventricles were chosen for assessment of periventricular white matter and 1 through the centrum semi-ovale was chosen for assessment of subcortical white matter (frontal and parietal lobes). The nonlinear transformation parameters were used to map the ROI onto the corresponding FA and MD images.

**Other Measurements**

We considered age, gender, height, and TBV as possible confounders. Because SVD is correlated with TBV, and because cerebral atrophy is a predictor of gait disturbance, this was also considered a possible confounder. We used the Mini-Mental State Examination score (range, 0–30) to assess global cognitive status. Functional independence was assessed using the Barthel Index (range, 0–20).

**Statistical Analysis**

The baseline characteristics were presented as mean±SD, and for the skewed distributed parameters the median and interquartile range were calculated. The quantitative GAITRite and semiquantitative Timed-Up-and-Go measures were averaged over 2 and 3 walks. When 1 trial was missing (n=5 for quantitative and n=2 for semiquantitative assessment), the remaining measures were used.

The relation between DTI parameters and gait was analyzed in 2 ways. First, we used multiple linear regression to investigate the relation between FA and MD in both the WML and NAWM and gait performance, with adjustment for age, gender, height, and TBV. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. We furthermore examined the association between TBV and gait, adjusted for age, gender, height, and WML. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. In positively skewed distributions, the log transformation was used. Regression coefficients were presented as standardized $\beta$ values. All data were analyzed using SPSS statistical software (version 16.0; SPSS).

**Results**

**Characteristics**

Gait assessment was available for 488 participants. Fifteen individuals could not participate because of walking aids (n=4), current levodopa use (n=1), drop foot (n=1), lower extremity amputation (n=1), joint fusion (n=2), severe arthritis (n=1), severe vascular problems of the lower extremity (n=2), or a psychogenic gait disturbance (n=3). Four subjects had to be excluded because of uninterpretable MRI sequences, yielding a final sample size of 484 subjects for this study.

**Statistical Analysis**

The baseline characteristics were presented as mean±SD, and for the skewed distributed parameters the median and interquartile range were calculated. The quantitative GAITRite and semiquantitative Timed-Up-and-Go measures were averaged over 2 and 3 walks. When 1 trial was missing (n=5 for quantitative and n=2 for semiquantitative assessment), the remaining measures were used.

The relation between DTI parameters and gait was analyzed in 2 ways. First, we used multiple linear regression to investigate the relation between FA and MD in both the WML and NAWM and gait performance, with adjustment for age, gender, height, and TBV. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. In positively skewed distributions, the log transformation was used. Regression coefficients were presented as standardized $\beta$ values. All data were analyzed using SPSS statistical software (version 16.0; SPSS).

**Results**

**Characteristics**

Gait assessment was available for 488 participants. Fifteen individuals could not participate because of walking aids (n=4), current levodopa use (n=1), drop foot (n=1), lower extremity amputation (n=1), joint fusion (n=2), severe arthritis (n=1), severe vascular problems of the lower extremity (n=2), or a psychogenic gait disturbance (n=3). Four subjects had to be excluded because of uninterpretable MRI sequences, yielding a final sample size of 484 subjects for this study.

**Statistical Analysis**

The baseline characteristics were presented as mean±SD, and for the skewed distributed parameters the median and interquartile range were calculated. The quantitative GAITRite and semiquantitative Timed-Up-and-Go measures were averaged over 2 and 3 walks. When 1 trial was missing (n=5 for quantitative and n=2 for semiquantitative assessment), the remaining measures were used.

The relation between DTI parameters and gait was analyzed in 2 ways. First, we used multiple linear regression to investigate the relation between FA and MD in both the WML and NAWM and gait performance, with adjustment for age, gender, height, and TBV. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. To investigate whether DTI parameters in the NAWM were associated with gait regardless of WML and number of lacunar infarcts, we additionally adjusted analyses for these parameters. In positively skewed distributions, the log transformation was used. Regression coefficients were presented as standardized $\beta$ values. All data were analyzed using SPSS statistical software (version 16.0; SPSS).

**Results**

**Characteristics**

Gait assessment was available for 488 participants. Fifteen individuals could not participate because of walking aids (n=4), current levodopa use (n=1), drop foot (n=1), lower extremity amputation (n=1), joint fusion (n=2), severe arthritis (n=1), severe vascular problems of the lower extremity (n=2), or a psychogenic gait disturbance (n=3). Four subjects had to be excluded because of uninterpretable MRI sequences, yielding a final sample size of 484 subjects for this study.
Table 2. Association Between Diffusion Tensor Imaging and Conventional MRI Parameters and Gait

<table>
<thead>
<tr>
<th>MRI Parameters</th>
<th>Gait Parameters</th>
<th>GAITrite Parameters</th>
<th>Clinical Rating Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Velocity (m/s)</td>
<td>Stride Length (m)</td>
<td>Cadence (steps/min)</td>
</tr>
<tr>
<td>White matter lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional anisotropy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.05</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean diffusivity (mm²/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>−0.15‡</td>
<td>−0.14‡</td>
<td>−0.13‡</td>
</tr>
<tr>
<td>Model 2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Normal-appearing white matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional anisotropy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.09‡</td>
<td>0.08†</td>
<td>0.09‡</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.02</td>
<td>−0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean diffusivity (mm²/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>−0.21§</td>
<td>−0.17§</td>
<td>−0.21§</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.12†</td>
<td>−0.06</td>
<td>−0.19†</td>
</tr>
<tr>
<td>Total brain volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>0.18§</td>
<td>0.18§</td>
<td>0.16‡</td>
</tr>
</tbody>
</table>

CV indicates coefficients of variation; NA, not applicable. Data are standardized β values. Model 1 is with adjustment for age, gender, height and total brain volume; model 2 is with additional adjustment for white matter lesions and N of lacunar infarcts; model 3 is with adjustment for age, gender, height, white matter lesion volume, and N of lacunar infarcts.

*For skewed variables the logarithm is presented.
†P<0.05.
‡P<0.01.
§P<0.001.

Table 1 shows the characteristics of the study population. Mean age was 65.6 years (SD, 8.9), with 43% being women. Median percentage NAWM of the whole white matter volume was high (98.5%; interquartile range, 96.0%–99.2%).

**MRI Parameters and Gait**

Subjects with a higher MD within the WML walked significantly slower (β = −0.15; P = 0.002) because of smaller steps (β = −0.14; P = 0.001) and a lower cadence (β = −0.13; P = 0.011), with a larger step width (β = 0.24; P < 0.001), a longer double-support percentage (β = 0.11; P = 0.039), a reduced stride width variability (β = −0.14; P = 0.010), and a trend to an increased stride time variability (β = 0.09; P = 0.081). There was also a significant relation between MD within WML and the Tinetti (β = −0.14; P = 0.008) and Timed-Up-and-Go test (β = 0.14; P = 0.004). However, a lower FA in the WML was only associated with a lower score on the Tinetti test (β = 0.10; P = 0.035; Table 2).

The relation between microstructural integrity and gait was not restricted to the WML, because there was also a significant relation between both DTI parameters in the NAWM and various quantitative and semiquantitative parameters of gait (Table 2). After additional adjustment for WML volume and number of lacunar infarcts, the association between MD in the NAWM and gait remained present, although weaker, for various parameters; however, this relation disappeared for FA.

Table 3 shows the results of the association between DTI parameters and gait velocity in 6 bilateral ROI. Despite the fact that the median percentage WML in the periventricular ROI was higher than in the subcortical ROI, we found in almost all ROI a significant association between high MD and low gait velocity and, to a lesser extent, between low FA and low gait velocity, also after Bonferroni correction. These relations disappeared after additional adjustment for WML volume and number of lacunar infarcts.

Apart from DTI parameters, conventional MRI parameters, such as TBV, were also found to be independently related to gait performance, with the exception of stride width variability (Table 2).

**Discussion**

In this large cohort of patients with cerebral SVD, we found that the microstructural integrity of both WML and NAWM, at multiple locations, was associated with gait performance. Major strengths of this study included its large sample size and use of novel imaging techniques such as DTI. Furthermore, our study is a single-center study with a high response rate, and all subjects were examined by only 2 investigators. We measured MD and FA using a whole brain voxel-based
Table 3. Association Between Diffusion Tensor Imaging Parameters in Regions of Interest and Gait

<table>
<thead>
<tr>
<th>Regions of Interest</th>
<th>Percentage White Matter Lesions (Interquartile Range)</th>
<th>Median</th>
<th>Fractional Anisotropy</th>
<th>Mean Diffusivity (mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standardized β Values</td>
<td>Standardized β Values</td>
</tr>
<tr>
<td>Periventricular</td>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Frontal L (A)</td>
<td>6.2 (0.6–20.4)</td>
<td>0.08</td>
<td>0.110</td>
<td>−0.14</td>
</tr>
<tr>
<td>Frontal R (A)</td>
<td>7.2 (1.9–22.8)</td>
<td>0.15</td>
<td>0.002*</td>
<td>−0.15</td>
</tr>
<tr>
<td>Frontal L (B)</td>
<td>15.0 (6.1–31.0)</td>
<td>0.16</td>
<td>0.001*</td>
<td>−0.14</td>
</tr>
<tr>
<td>Frontal R (B)</td>
<td>11.8 (5.1–26.6)</td>
<td>0.08</td>
<td>0.084</td>
<td>−0.11</td>
</tr>
<tr>
<td>Temporal L (A)</td>
<td>0.1 (0.0–9.5)</td>
<td>0.09</td>
<td>0.040</td>
<td>−0.12</td>
</tr>
<tr>
<td>Temporal R (A)</td>
<td>0.9 (0.0–13.6)</td>
<td>0.15</td>
<td>&lt;0.001*</td>
<td>−0.17</td>
</tr>
<tr>
<td>Occipital L (B)</td>
<td>7.6 (0.0–28.8)</td>
<td>0.13</td>
<td>0.008*</td>
<td>−0.14</td>
</tr>
<tr>
<td>Occipital R (B)</td>
<td>20.7 (4.2–41.7)</td>
<td>0.17</td>
<td>&lt;0.001*</td>
<td>−0.15</td>
</tr>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal L (C)</td>
<td>0.0 (0.0–2.1)</td>
<td>0.06</td>
<td>0.153</td>
<td>−0.13</td>
</tr>
<tr>
<td>Frontal R (C)</td>
<td>0.0 (0.0–2.9)</td>
<td>0.09</td>
<td>0.028</td>
<td>−0.16</td>
</tr>
<tr>
<td>Parietal L (C)</td>
<td>0.0 (0.0–1.0)</td>
<td>0.00</td>
<td>0.926</td>
<td>−0.19</td>
</tr>
<tr>
<td>Parietal R (C)</td>
<td>0.0 (0.0–2.0)</td>
<td>0.06</td>
<td>0.118</td>
<td>−0.18</td>
</tr>
</tbody>
</table>

L indicates left; R, right.
Adjusted for age, gender, height, and total brain volume.
Regions of interest were placed at different axial planes (A, B, C) as shown in the Figure.
*Significant after Bonferroni correction.

Within the WML, we found a relation between high MD and worse score on almost all gait parameters. This may indicate that otherwise identical-appearing WML on FLAIR imaging reflect different microstructural abnormalities and subsequently have different consequences for gait performance. It should be noted that we did not account for the spatial distribution of WML, which was not entirely comparable between all subjects. Because the networks involved in the control of gait are considered to be widespread,8 which is in line with our findings in the ROI analysis that loss of microstructural integrity at multiple locations was related to a lower gait velocity, we feel that this has not greatly influenced our results. However, other studies have shown that not all locations are even important in relation to gait. A recent study used partial least-square regression to investigate the effect of WML location independent of other WML locations and found the frontal WML to be most related to poorer gait.7 It would be interesting to apply this technique in DTI analysis in future studies.

The MD, which reflects the magnitude of the diffusion of water, within the WML was found to be more strongly related to gait than the FA, which measures the directionality of the diffusion of water. One explanation could be that both parameters reflect different pathophysiology with different consequences for gait performance. The disparity in associations also could be explained by the differences in WML location between subjects, because FA values vary widely across the whole white matter in the normal brain.12 Multiple fibers are present within a single voxel and may have all different destinations. Because of this intravoxel fiber incoherence, the measured FA within a given voxel may be low.

analysis differentiating between WML and NAWM, as well as ROI analysis, to provide global and regional information of the microstructural integrity in relation to gait. Another strength is the manual segmentation of WML and quantitative assessment of gait. Moreover, we were able to investigate the effect of microstructural integrity on gait independently of TBV and in the NAWM also independently of WML volume and lacunar infarcts. We intentionally did not correct for vascular risk factors, such as hypertension or diabetes, because they were considered part of the causal chain between SVD and gait performance. Another methodologic issue is the term SVD, which is used in different contexts (ie, pathological, neuroimaging, and clinical aspects). As mentioned, neuroimaging has a central role in defining SVD. WML and lacunar infarcts are widely accepted signs of cerebral SVD. However, WML also may be caused by other diseases. Lacunar infarcts also may result from non-SVD-related mechanisms, such as embolism from the heart or proximal arteries.31 Therefore, we cannot rule out some misclassification of lacunar infarcts as SVD-related in our study. Because the majority of lacunar strokes are SVD-related31 and the lacunar infarcts in our study were all accompanied by some degree of WML, favoring an underlying SVD-related mechanism,32 we feel that this misclassification would be rather small and would not greatly influence our results. Finally, an important limitation is the cross-sectional nature of our study, which prevents us from proving causality. The RUN DMC study has a longitudinal design to evaluate the effect of progression of SVD on (changes in) gait.
and does not necessarily reflect an underlying lower microstructural integrity. In contrast, MD is not so much affected by fiber crossing and remains relatively constant throughout the white matter.12

We furthermore found that the association between loss of microstructural integrity of the white matter and gait extended even in the NAWM, which constituted the largest part of the white matter in our study. Hence, our findings imply that the microstructural integrity of the NAWM also should be taken into account when investigating the relation between SVD and gait. This is in line with 2 other smaller studies finding that the microstructural integrity of the corpus callosum, a structure typically free from SVD, is associated with gait.14,15 The contribution of damage to the NAWM also recently was found in relation to cognitive impairment,33 another symptom of SVD.

Because most associations in the NAWM disappeared or weakened after additional control for WML and lacunar infarcts, it seems plausible that SVD is one of the underlying pathological mechanisms in the relation between microstructural integrity of NAWM and gait. When interpreting these results, it is important to consider that the severity of damage in the NAWM is positively associated with the WML load.34 Several explanations therefore could be proposed by which SVD may be related to the associations between the microstructural integrity of the NAWM and gait. First, it may be that these associations were, at least in part, explained by the coexisting WML, and not so much by the loss of the microstructural integrity of the NAWM. Second, it could be that WML and DTI changes in the NAWM share similar risk factors for SVD, such as hypertension;35 additional control for WML and lacunar infarcts therefore will reduce the magnitude of the association between DTI parameters in NAWM and gait. Finally, WML may lead to axonal loss in areas (ie, the NAWM) connected by axons that travel through these WML by anterograde (Wallarian) or retrograde neuronal degeneration. However, some associations in the NAWM (eg, with cadence) did not alter after additional control for WML and lacunar infarcts. This indicates that factors other than SVD also may play a role. Future studies are needed to explore these processes and hence the relevance of damage to the NAWM in gait disturbances in SVD in more detail. Finally, we found that a smaller TBV was associated with poorer gait performance, suggesting that patients with SVD also may be more vulnerable to gait disturbances related to global brain atrophy.

Conclusion

In conclusion, this study indicates that loss of microstructural integrity not only within WML but also of the NAWM contributes to gait disturbances. DTI led to considerable insight into the pathogenesis of gait disturbances in persons with SVD. Whether DTI-derived metrics are a better marker for gait disturbances in patients with SVD than those of conventional MRI (WML, lacunar infarcts, TBV) should be investigated in future studies. Future studies are needed to establish the regional correlates of white matter integrity and gait more specifically by using whole brain analysis with region-specific information such as tract-based spatial statistics. Furthermore, they should be prospective to assess causality and to investigate if changes in the microstructural integrity of the NAWM are treatable and preventable by treatment of risk factors for SVD, such as with blood pressure-lowering agents.

Sources of Funding

Dr de Leeuw received a personal fellowship of the Dutch Brain foundation (H04-12) and a clinical fellowship of the Netherlands Organization for Scientific Research (project number 40-00703-97-07197).

Disclosures

None.

References


Diffusion Tensor Imaging and Gait in Elderly Persons With Cerebral Small Vessel Disease
Karlijn F. de Laat, Anouk G.W. van Norden, Rob A.R. Gons, Lucas J.B. van Oudheusden, Inge W.M. van Uden, David G. Norris, Marcel P. Zwiers and Frank-Erik de Leeuw

Stroke. 2011;42:373-379; originally published online December 30, 2010;
doi: 10.1161/STROKEAHA.110.596502

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/2/373

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/