Microbleeds Are Independently Related to Gait Disturbances in Elderly Individuals With Cerebral Small Vessel Disease

Karlijn F. de Laat, MD; Heleen A.C. van den Berg, BSc; Anouk G.W. van Norden, MD; Rob A.R. Gons, MD; Marcel G.M. Olde Rikkert, MD, PhD; Frank-Erik de Leeuw, MD, PhD

Background and Purpose—Cerebral small vessel disease (SVD), including white matter lesions and lacunar infarcts, is related to gait disturbances. Microbleeds (MB) are another manifestation of SVD, but their clinical impact remains unclear. We therefore investigated the relation between the number and location of MB and gait, independently of white matter lesions and lacunar infarcts.

Methods—MRI scanning was performed in 485 nondemented elderly individuals with cerebral SVD. The number and location of MB were rated. Gait was assessed with a GAITRite system and the Tinetti and Timed-Up-and-Go tests. MB were related to gait parameters by age, height, total brain volume, white matter lesions, and number of lacunar infarcts-adjusted linear regression.

Results—A higher number of MB was independently related to a shorter stride length and poorer performance on the Tinetti and Timed-Up-and-Go tests. These relations seemed to be explained by MB in the temporal and frontal lobe and basal ganglia, including the thalamus.

Conclusions—This study offers the first indication that MB may be associated with gait disturbances, independently of other coexisting markers of SVD. (Stroke. 2011;42:494-497.)

Key Words: cerebral small vessel disease / gait / microbleeds

Cerebral small vessel disease (SVD), including white matter lesions (WML) and lacunar infarcts, adversely affects gait. Cerebral microbleeds (MB) are increasingly being recognized as another manifestation of cerebral SVD. However, the consequences of MB are largely unknown. They are generally considered clinically silent, although some recent studies showed a relation between MB and cognitive disturbances. Whether these associations can be attributed to a direct effect of MB or to the accompanying WML and lacunar infarcts remain incompletely understood. As far as we know, the relation between MB and gait disturbances has never been studied. We hypothesized that MB were associated with gait disturbances, preferentially in regions related to the control of gait, such as the frontal lobe and basal ganglia. We therefore cross-sectionally investigated the association between MB, their location, and gait in elderly individuals with cerebral SVD.

Subjects and Methods

Study Population
The Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUN DMC) study is a prospective cohort study that investigates risk factors and clinical consequences of brain changes as assessed by MRI among nondemented elderly individuals with cerebral SVD referred to our department. A total of 503 participants, aged between 50 and 85 years, were enrolled in the original cohort. For the present study, those with inability to walk 6 m unaided (n=4), current levodopa use (n=1), conditions that affected gait performance (n=10), or an uninterpretable MRI (n=3) were additionally excluded, yielding a final sample size of 485 subjects.

MRI
Standardized T1- and T2-weighted and gradient-echo T2*-weighted sequences (repetition time/echo time, 800/26 ms; voxel size, 1.3×1.0×5.0 mm; interslice gap, 1.0 mm) were acquired. WML (mL), lacunar infarcts (n), territorial infarcts (n) (diameter ≥15 mm in known arterial territories), and total brain volume (mL) were assessed according to a standardized protocol. The number of MB were rated by 2 trained raters according to recently formulated criteria and categorized into a lobar, deep, or infratentorial location. In a random sample of 10%, intrarater and inter-rater reliability for the total number of MB yielded an intraclass correlation coefficient of 0.79 and 0.99; inter-rater reliability for the number in individual locations was 0.94 to 1.00.

Gait
As reported previously, we measured gait velocity, stride length, cadence, stride width, and double support percentage using the 5.6-m...
GAITRite system (MAP/CIR). In addition, we used the Tinetti and Timed-Up-and-Go tests.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 16.0. Because the number of MB was positively skewed, we changed the 2 highest scores (15 and 32) into the next highest score10 to reduce the skewness to some extent. Other methods to reduce the skewness, such as log transformation, did not change the presented associations. The relation between the number of MB and gait was investigated using multiple linear regression analysis adjusted for age, gender, height, total brain volume, and number of territorial infarcts. We subsequently adjusted for WML volume (log-transformed) and the number of lacunar infarcts. Second, the effect of the location of MB was studied adjusted for the aforementioned covariates and in the second model, also, for the remaining MB at other locations. Bonferroni correction was applied by adjusting the significance level to 0.05/9=0.0056. The location was furthermore studied in 4 groups (no MB, strictly lobar, deep/infratentorial, and mixed) using analysis of covariance adjusted for age, gender, height, total brain volume, number of territorial and lacunar infarcts, and WML volume. Finally, we studied whether results changed when we additionally excluded subjects with territorial infarcts.

**Results**

**Characteristics**

Characteristics of the study population are shown in Table 1. The prevalence of MB was 10.7% (52/485). Of those with MB, 48.1% (95% CI, 43.7–52.5) had 1 MB, 21.1% (95% CI, 17.5–24.7) had 2 MB, 15.4% (95% CI, 12.2–18.6) had 3 to 5 MB, and 15.4% (95% CI, 12.2–18.6) had >5 MB. Thirty-one (59.6%) individuals exhibited MB only in lobar areas and 7 (13.5%) had them in a strictly deep/infratentorial location.

The number of MB and territorial infarcts were not significantly related to each other (Pearson correlation coefficient=0.02). Additional exclusion of subjects with territorial infarcts did not change the presented associations.

**MB and Gait**

A higher number of MB was associated with a lower gait performance (Table 2). After additional adjustment for WML and lacunar infarcts, MB were still related to a shorter stride length (standardized $\beta=-0.09$; $P=0.016$) and borderline significant to a longer double-support percentage (standardized $\beta=0.08$; $P=0.067$). The independent relation between MB and gait disturbances was even more pronounced for the clinical rating scales (Table 2).

**Location of MB and Gait**

MB in the frontal and temporal lobe and basal ganglia were significantly related to a shorter stride length and also to a lower gait velocity in the temporal lobe (Table 3), even after adjustment for the number of MB at other sites. A lower score on both clinical rating scales was also significantly related to MB in the thalamus.

When subjects with MB were divided into 3 groups (strictly lobar, deep/infratentorial, and mixed), subjects with mixed MB had a significantly shorter stride length (mean, 1.25 m; $P=0.007$) and a longer Timed-Up-and-Go test (mean, 10.86 sec; $P=0.005$) than those without MB (mean, 1.39 m and 9.08 sec). This was also true for persons with strictly deep/infratentorial MB (mean, 1.30 m and $P=0.189$; and mean, 10.59 sec and $P=0.071$), although not significant. In contrast, subjects with strictly lobar MB, the largest group, did not differ from those without MB.

**Discussion**

We found that the number of MB, especially those located in the frontal lobe, temporal lobe, and basal ganglia (and thalamus), interfered with gait independent of coexisting WML and lacunar infarcts. Strengths of our study included the large sample size and quantitative assessment of gait. Moreover, we were able to investigate the effect of MB on
gait independently of WML, segmented manually, on infarcts and total brain volume. We intentionally did not adjust for vascular risk factors such as hypertension because they were considered an earlier part of the causal chain between MB and gait performance. However, interpretation of our results regarding cause and effect is limited because of the cross-sectional design. Second, because recent MRI techniques have improved the detection of MB,7 we may have underestimated the actual number of MB. This probably may have led to a systematic measurement error that may have affected the effect size, but not our observation of an association between MB and gait.

MB were independently related to a shorter stride length and poorer scores on the clinical rating scales. We furthermore found that their location played a role in these associations, independently of coexisting WML or lacunar infarcts. These findings, together with results from pathological studies showing that MB are frequently characterized by surrounding microstructural damage,9 suggest that they have a direct effect on motor performance rather than simply reflecting the presence of other markers of SVD.

We found that MB in the basal ganglia, the thalamus, and frontal lobe, which are areas involved in the control of gait,10 were related to gait disturbances. This is in line with our earlier report1 on the relation between the presence of other markers of SVD, WML, and lacunar infarcts in these regions and gait disturbances. The relation between MB in the temporal lobe, which is involved in processing visual and vestibular signals, and gait performance is also in accordance with functional imaging studies of normal gait.10 This finding is interesting because the temporal lobe is not a predilection site for WML11 and therefore may indicate much more widespread disruption of neuronal networks in subjects with SVD and gait disturbances than previously thought based on conventional T2-weighted images.

It is suggested that strictly lobar-located MB are attributable to amyloid angiopathy, whereas MB in deep/infratentorial regions (with or without lobar MB) rather represent hypertensive microangiopathy.8 Our findings therefore are suggestive of hypertensive SVD as the underlying etiology, although we have to note that these results should be interpreted with caution (the mean number of MB in the

Table 2. Association Between Number of Microbleeds and Gait

<table>
<thead>
<tr>
<th>N of Microbleeds</th>
<th>Gait Velocity (m/sec)</th>
<th>Stride Length (m)</th>
<th>Cadence (Steps/min)</th>
<th>Stride Width (cm)</th>
<th>Double-Support Percentage (%)</th>
<th>GAITRite Parameters</th>
<th>Clinical Rating Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>−0.04/−0.16*</td>
<td>−0.03/−0.17†</td>
<td>−0.65/−0.08</td>
<td>0.31/0.12*</td>
<td>0.55/0.16†</td>
<td>−0.24/−0.23†</td>
<td>0.02/0.21†</td>
</tr>
<tr>
<td>Model 2</td>
<td>−0.03/−0.12*</td>
<td>−0.02/−0.14*</td>
<td>−0.45/−0.05</td>
<td>0.27/0.11*</td>
<td>0.46/0.14*</td>
<td>−0.22/−0.21†</td>
<td>0.02/0.17†</td>
</tr>
<tr>
<td>Model 3</td>
<td>−0.01/−0.07</td>
<td>−0.02/−0.09*</td>
<td>−0.07/−0.01</td>
<td>0.12/0.05</td>
<td>0.28/0.08</td>
<td>−0.18/−0.17†</td>
<td>0.01/0.14*</td>
</tr>
</tbody>
</table>

Data are regression coefficients/standardized β values. Compares the unadjusted relation between the N of microbleeds and gait; model 2 is with adjustment for age, gender, height, total brain volume, and the N of territorial infarcts; and model 3 is with additional adjustment for white matter lesion volume and the N of lacunar infarcts.

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

Table 3. Association Between Location of Microbleeds and Gait

<table>
<thead>
<tr>
<th>N of Microbleeds</th>
<th>Gait Velocity (m/sec)</th>
<th>Stride Length (m)</th>
<th>Cadence (Steps/min)</th>
<th>GAITRite Parameters</th>
<th>Clinical Rating Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td>−0.01/−0.05</td>
<td>−0.02/−0.07</td>
<td>−0.03/0.00</td>
<td>−0.20/−0.16*</td>
<td>0.01/0.11*</td>
</tr>
<tr>
<td>Frontal</td>
<td>−0.06/−0.09</td>
<td>−0.06/−0.12*</td>
<td>−0.38/−0.01</td>
<td>−0.71/−0.23*</td>
<td>0.05/0.17*</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.00/0.01</td>
<td>−0.00/0.00</td>
<td>0.54/0.02</td>
<td>−0.14/−0.05</td>
<td>0.01/0.03</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.04/0.04</td>
<td>0.03/0.04</td>
<td>0.89/0.03</td>
<td>0.18/0.05</td>
<td>−0.01/−0.04</td>
</tr>
<tr>
<td>Temporal</td>
<td>−0.14/−0.12*</td>
<td>−0.14/−0.15*</td>
<td>−2.74/−0.06</td>
<td>−1.36/−0.26*</td>
<td>0.09/0.20*</td>
</tr>
<tr>
<td>Deep</td>
<td>−0.05/−0.08</td>
<td>−0.05/−0.11*</td>
<td>0.67/0.03</td>
<td>−0.67/−0.20*</td>
<td>0.04/0.14*</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>−0.13/−0.07</td>
<td>−0.16/−0.11*</td>
<td>2.01/0.02</td>
<td>−1.64/−0.20*</td>
<td>0.10/0.15*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>−0.03/−0.03</td>
<td>−0.04/−0.05</td>
<td>0.79/0.02</td>
<td>−0.68/−0.17*</td>
<td>0.03/0.10*</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>−0.01/−0.02</td>
<td>−0.01/−0.03</td>
<td>0.11/0.01</td>
<td>−0.02/−0.01</td>
<td>0.01/0.07</td>
</tr>
</tbody>
</table>

Data are regression coefficients/standardized β values. Adjusted for age, gender, height, total brain volume, the N of territorial infarcts and lacunar infarcts, and white matter lesion volume.

*Significant after Bonferroni correction (P<0.006).
†For skewed variables the logarithm is presented.
mixed group was higher than in the other 2 groups with equal number of MB).

**Conclusion**

In conclusion, this study offers the first indication to our knowledge that cerebral MB may contribute to gait disturbances, independently of other coexisting markers of SVD. Other studies are needed to replicate these findings.

**Sources of Funding**

F.E.d.L. 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**


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Stroke. 2011;42:494-497; originally published online December 16, 2010; doi: 10.1161/STROKEAHA.110.596122
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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