Frontal and Temporal Microbleeds Are Related to Cognitive Function

The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study

Anouk G.W. van Norden, MD; Heleen A.C. van den Berg, BSc; Karlijn F. de Laat, MD; Rob A.R. Gons, MD; Ewoud J. van Dijk, MD; Frank-Erik de Leeuw, MD

Background and Purpose—Cerebral small vessel disease, including white matter lesions and lacunar infarcts, is related to cognitive impairment. Cerebral microbleeds (MBs) are increasingly being recognized as another manifestation of small vessel disease and are also related to cognitive function. However, it remains unclear whether this relation is independent of white matter lesions and lacunar infarcts and if location of MB plays a role. We investigated the relation between the presence, number, and location of MB and cognitive performance adjusted for white matter lesions and lacunar infarcts.

Methods—Presence, number, and location of MB were rated on a gradient echo T2*-weighted MRI in 500 nondemented elderly patients with small vessel disease. Cognitive performance was assessed in different domains. Analyses were adjusted for age, sex, education, depressive symptoms, total brain volume, white matter lesion volume, and lacunar and territorial infarcts.

Results—Mean age was 65.6 years (SD 8.8) and 57% were male. MBs were present in 10.4% of the participants. Subjects with MBs were significantly older, had a higher white matter lesion volume, and more lacunar infarcts (P<0.001). Presence and number of MBs were related to global cognitive function (β−0.10, P=0.008; β−0.20, P=0.002), psychomotor speed (β−0.10, P=0.012; β−0.19, P=0.006), and attention (β−0.10, P=0.02; β−0.205, P=0.001). The relations with cognitive performance were mainly driven by frontal, temporal, and strictly deep located MB.

Conclusions—Frontal and temporal located MBs correlate with cognitive performance in nondemented elderly patients independent of coexisting other small vessel disease-related lesions. MBs are clinically not silent and may help to understand the role of vascular disease in cognitive decline. (Stroke. 2011;42:3382-3386.)

Key Words: cerebral microbleeds ■ cognition ■ small vessel disease

Cerebral small vessel disease (SVD) related lesions, including white matter lesions (WMLs) and lacunar infarcts, are common in the elderly. Cerebral SVD is an important cause of cognitive impairment in elderly, eventually leading to dementia in some.1,2 Cerebral microbleeds (MBs) are increasingly recognized as another manifestation of SVD.3,4 Radiologically they are characterized as small, homogeneous, round foci of low signal intensity on gradient-echo T2* sequences. Histopathologic analysis shows that these are perivascular collections of hemosiderin deposits.5 Accumulating evidence suggests that the distribution of MB may reflect the underlying pathological changes, lobar MBs are presumably attributable to cerebral amyloid angiopathy, whereas MBs in the deep/infratentorial regions are considered to represent hypertensive microangiopathy.4,6,7 Although considered to be clinically silent, MBs have been related to cognitive impairment.8–10 This has predominantly been investigated in memory clinic patients, usually without taking location of MB into account and without quantitative WML adjustment.11 Because MBs virtually always coexist with WML and lacunar infarcts, its relation with cognitive performance should be assessed independent of manually segmented WML and number of lacunar infarcts at different lobar and deep locations. Due to the typical profile of “subcortical” cognitive impairment in patients with SVD with psychomotor slowing due to impaired executive function, deficits of attention, planning and set-shifting, and episodic memory disturbances,12 we hypothesized that MBs in frontal and temporal regions have the strongest relation with cognitive function. Therefore, we wanted to investigate the relation
between the presence, number, and location of MB and cognitive performance independent of coexisting WML and lacunar infarcts.

Materials and Methods

Study Population

The Radboud University Nijmegen Diffusion tensor and Magnetic resonance Cohort (RUNDMC) study prospectively investigates the risk factors and clinical consequences of brain changes as assessed by MRI among 503 50- to 85-year-old nondemented elderly patients with cerebral SVD.13

On the basis of established research criteria, SVD was defined as the presence of WMLs and/or lacunar infarcts.1 Symptomatic MBs were excluded—MBs include acute symptoms such as transient ischemic attacks or lacunar syndromes or subacute manifestations such as cognitive, motor (gait) disturbances, and/or depressive symptoms.12 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.14 Accordingly, in 2006, consecutive patients referred to the Department of Neurology between October 2002 and November 2006 were selected for participation. Inclusion criteria were: (1) age between 50 and 85 years; and (2) cerebral SVD on neuroimaging (WML and/or lacunar indicators). Patients were selected for participation by a 3-step approach. After reviewing medical records, 1004 individuals were invited by letter; 727 were eligible after contact by telephone of whom 525 agreed to participate. During these 3 steps, patients excluded because of dementia were diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, Version IV,15 with formal cognitive assessment. First, patients were excluded based on the clinical information and cognitive assessment obtained by reviewing the medical records. Second, during contact by telephone, patients were excluded when a close informant told us that the eligible person was excluded because of dementia if they fulfilled the previously mentioned criteria (n=4). In 18 individuals, 1 of the other exclusion criteria was found during their visit to our research center, yielding a response rate of 71.3% (503 of 705).

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

Magnetic Resonance Imaging

All subjects underwent a 1.5-T MRI. The protocol included, among other sequences, 3-dimensional T1 magnetization-prepared rapid gradient-echo (TR/TE/TI 2250/3.68/850 ms; flip angle 15°; voxel size 1.0×1.2×5.0 mm, interslice gap 1 mm), and transversal T2*-weighted gradient echo sequences (TR/TE 800/26 ms; voxel size 1.3×1.0×6.0 mm; interslice gap 1 mm).7

MRI Analysis

WMLs and Lacunar and Territorial Infarcts

White matter signal hyperintensities on fluid-attenuated inversion recovery images, which were not, or only faintly, hypointense on T1-weighted images, were considered WML, except for glissoid-surrounding infarcts.17 WMLs were manually segmented on fluid-attenuated inversion recovery images by 2 trained raters. Total WML volume was calculated by summing the segmented areas multiplied by slice thickness. Lacunar infarcts were defined as hypointense areas with a diameter >2 mm and <15 mm with low signal intensity on T1 and fluid-attenuated inversion recovery, ruling out enlarged perivascular spaces and infraputaminal pseudolacunes.17 All imaging analyses were performed by raters blinded to clinical information. In a random sample of 10%, interrater variability for total WML volume yielded an intraclass correlation coefficient of 0.99; intra- and interrater reliability for the lacunar infarcts yielded a weighted κ of 0.80 and 0.88. Territorial infarcts are defined as hypointense on fluid-attenuated inversion recovery and T1 images >15 mm.17 Microbleeds

MBs are defined as small, homogeneous, round focal areas of very low signal intensity on T2*-weighted images of <10 mm in diameter.4,8 They were categorized in lobar (cortical gray and subcortical or periventricular white matter), deep (deep gray matter, including the basal ganglia and thalamus, the white matter of the corpus callosum, internal, external, and extreme capsule), and infratentorial (brain stem and cerebellum).4,8 Lesions are not considered to be MBs when they are symmetrical hypointensities in the globus pallidus, most likely calcifications or iron deposits, flow void artifacts of the pial blood vessels, or hypoglycins in T2* inside a lesion, compatible with an infarct, likely to be hemorrhagic transformation.4,8 MBs were rated by 2 trained raters, in a 10% random sample; intra- and interrater reliability yielded an intraclass correlation coefficient of 0.79 and 0.99 for total number of MBs and 0.94 and 1.00 for individual locations.

Total Brain Volume and Intracranial Volume

Gray and white matter tissue and cerebrospinal fluid probability maps were computed using SPM5 unified segmentation routines on the T1 magnetization-prepared rapid gradient-echo images (Wellcome Department of Cognitive Neurology, University College London, London, UK). Total gray matter, white matter, and cerebrospinal fluid volumes were calculated by summing all voxel volumes that had a P<0.5 for belonging to the tissue class. Total brain volume was taken as the sum of total gray matter and WM. Intracranial volume was a summation of all tissue classes, that is, total gray matter, white matter, and cerebrospinal fluid volume. To normalize for head size, total brain volume was expressed as a percentage of total intracranial volume.

Measurement of Cognitive Function

Cognitive function was measured with a neuropsychological test battery that proved to be sensitive and suitable for this purpose in other, large epidemiological studies.1 The tests used are described in detail elsewhere.13 In short, we calculated compound scores for 7 cognitive domains. Global cognitive function was evaluated by the Mini Mental State Examination and the Cognitive Index. The Cognitive Index is a compound score that was calculated as the mean of the z-scores of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the mean of the reading subtask of the Stroop test, the mean of the Symbol–Digit Substitution Task, and the mean of the added score on the 3 learning trials of the Rey Auditory Verbal Learning Test and the delayed recall of this last test.1 Verbal memory is a compound score of the mean of 2 z-scores from the Rey Auditory Verbal Learning Test, 1 for the added scores of the 3 learning trials of this test and 1 for the delayed recall of this test. Visuospatial memory is a compound score of the mean of the z-scores of the immediate recall trial and the delayed recall trial of the Rey Complex Figure Test. Psychomotor speed was calculated as the mean of the z-scores of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the reading subtask of the Stroop test, and the Symbol–Digit Substitution Task.1 Fluency was calculated from the mean of the z-scores of both verbal fluency tasks. Concept shifting was calculated as the z-score of the third subtask of the Stroop. Attention is a compound score of the z-score of the total time of the Verbal Series Attention Test.1
Other Measurements

Age, sex, education, depressive symptoms, WML volume, lacunar infarcts, territorial infarcts, and normalized total brain volume were considered possible confounders. Depressive symptoms were present if a subject had a score $\geq 16$ on the Center of Epidemiological Studies on Depression Scale and/or the present use of antidepressive medication.18

For assessment of vascular risk factors, structured questionnaires were used together with measurements of blood pressure taken on separate occasions. The risk factors included presence of hypertension (mean blood pressure $\geq 140/90$ mm Hg and/or use of antihypertensive medications), diabetes (treatment with antidiabetic medications), hypercholesterolemia (treatment with lipid-lowering drugs), and smoking status.

Statistical Analysis

Baseline characteristics were presented as means±SD and for the skewed distributed parameters, the median and interquartile range were calculated. Baseline characteristics were compared between subjects with and without MB by age- and sex-adjusted analysis of covariance.

The relation between the presence and number of MBs and cognitive performance was investigated using multiple linear regression analysis adjusted for age, sex, education, depressive symptoms, WML volume, number of lacunar infarcts, territorial infarcts, and total brain volume normalized for head size.13

Second, the relation between the location of MB and cognitive performance was studied both in the previously described model and next with adjustments for MB at other locations. Bonferroni corrections were applied.

The relation between location and cognitive performance was also investigated with the subjects divided into 4 groups (no MB, strictly lobar, deep/infratentorial, and mixed) using analysis of covariance adjusting for the same covariates.

Results

For the present study, 3 subjects were excluded because of MRI artifacts, resulting in a final study population of 500 subjects. MBs were present in 10.4% of the population, 48.1% had 1 MB, 21.1% had 2 MBs, 15.4% had 3 to 5 MBs, and 15.4% had $\geq 5$ MBs. Thirty-one (59.6%) individuals had strictly lobar MB and 7 (13.5%) had isolated deep/infratentorial MB. Subjects with MB were significantly older ($P<0.001$), had a higher WML volume ($P<0.001$), and a higher proportion of subjects with MB had lacunar infarcts compared with those without MB ($P<0.001$; Table 1).

The presence of MB was related to the Cognitive Index, psychomotor speed, and attention. A higher number of MBs was independently related to a lower performance on cognitive performance (Table 2).

The relation between MB and cognitive performance was mainly driven by frontal and temporal located MB. Deep MBs were related to global cognitive function, psychomotor speed, and attention (Table 3). Additional adjustment for MBs at other locations did not alter the magnitude of the relations.

Only those with strictly deep and mixed MB performed worse on global cognitive function ($P=0.013$), psychomotor speed ($P=0.002$), and attention ($P=0.001$) compared with those without MB.

Discussion

The presence and number of MBs, especially those located in the frontal and temporal lobe, but also strictly deep located...
MBs, interfere with cognitive performance independent of other manifestations of SVD.

The relation between MB and cognitive performance has been demonstrated before in population-based cohorts, memory clinic cohorts, and a cohort from a neurovascular clinic.11 Strong elements of our study are that we examined for the first time the effect of MB at different lobar and at deep locations independent of quantitatively assessed WML rather than a semiquantitative assessment, in which a ceiling effect of this other parameter of SVD could result in residual confounding. Furthermore, we extensively adjusted for other possible confounders. We intentionally did not adjust for vascular risk factors such as hypertension because they were considered to be an earlier part of the causal chain between MB and cognitive performance. Finally, other major strengths of our study included the large sample size, the extensive assessment of cognitive function, the single-center design, the use of a single scanner, and the high response rate.

A limitation is the cross-sectional nature of the study, which prevented us from proving causality. Furthermore, MRI techniques on the detection of MB have improved, which may have resulted in underestimation of the actual number of MB in our population, which may have affected the effect size but not the association with cognitive performance.3 However, a recent study on the clinical relevance of the improved detection techniques for MB in terms of associations with clinical characteristics, vascular risk factors, and other MRI markers of SVD did not find stronger relations (or more variance explained) between cognition and MB detected with susceptibility-weighted imaging compared with T2*-weighted imaging.19

We found that MBs were related to cognitive performance independent of WML and lacunar infarcts. Furthermore, location played a role in the associations. These findings, together with results from pathological studies showing that MBs are frequently characterized by surrounding microstructural damage,20 suggest that they have a direct effect on cognitive performance rather than simply reflecting the presence of other markers of SVD, because our findings are independent of WML volume and lacunar infarcts.

It is hypothesized that the distribution of MB reflects the underlying etiology. Lobar MBs have been attributed to cerebral amyloid angiopathy, whereas MBs in the deep/infratentorial regions (with or without lobar MB) have been associated with hypertensive microangiopathy.4,6,7 We found that the relation between MB and lower cognitive performance was mainly driven by MBs located in the frontal and temporal lobes. A recent report on the distribution of lobar MB taking lobar volumes and clustering effects into account found that lobar MBs are significantly more often located in the temporal lobe.21 This suggests that the relation observed between temporal located MB and lower cognitive performance might, at least in part, be explained by the higher number of MBs in this region compared with other regions if...
one would take the volume of the temporal lobe into account. Because the temporal lobe is known to be more affected by cerebral amyloid angiopathy, our findings are therefore suggestive of cerebral amyloid angiopathy as an underlying etiology. However, we also found a relation between the strictly deep located MBs and lower cognitive performance, favoring multiple causes rather than a single cause for cognitive impairment in patients with MB (and SVD).

The underlying mechanisms of the pathological association between MB and cognitive function are unknown. However, histopathologic studies have shown that the presence of MB indicates widespread damage of arterioles by hypertension or by amyloid deposition as well as surrounding gliosis or even frank necrosis or infarction, resulting in microstructural damage of the surrounding white matter.\(^5\)\(^6\) In this way, MBs may disrupt white matter tracts relevant for cognitive function leading to damage to the neural networks superimposed to the effects of often co-occurring WML and lacunar infarcts. This tissue damage, not visible on conventional MRI, can be assessed in future studies with rather new techniques such as diffusion tensor imaging or resting state MRI.

In conclusion, we found that the presence and number of cerebral MBs independent of coexisting WML and lacunar infarcts correlate with cognitive performance in nondemented elderly patients; this relation is mainly driven by the frontal and temporal located MBs, but also by strictly deep located MBs. These results suggest that MBs are clinically not as silent as they are considered to be and in that way might help us to understand the role of vascular disease in cognitive decline. Follow-up should identify whether the presence at baseline and/or increase of MB over time predicts future cognitive decline and development of dementia and whether location of these MBs plays a role in this relation.

Sources of Funding

F.E.d.L and E.J.v.D. received personal fellowships from the Dutch Brain Foundation (H04–12; F2009[1]–16); a clinical fellowship from the Netherlands Organizational Scientific Research (40-00703-97-07197), and “Internationale Stichting Alzheimer Onderzoek.”

Disclosures

None.

References

Frontal and Temporal Microbleeds Are Related to Cognitive Function: The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study
Anouk G.W. van Norden, Heleen A.C. van den Berg, Karlijn F. de Laat, Rob A.R. Gons, Ewoud J. van Dijk and Frank-Erik de Leeuw

Stroke. 2011;42:3382-3386; originally published online September 22, 2011; doi: 10.1161/STROKEAHA.111.629634

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/42/12/3382

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/