Microbleeds do not affect rate of cognitive decline in Alzheimer disease

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ABSTRACT

Objective: To investigate the relationship between brain microbleeds (MBs) and the rate of cognitive decline in Alzheimer disease (AD).

Methods: In this cohort study, we studied 221 patients with AD with available baseline MRI scans (1.0 or 1.5 T) and at least 2 Mini-Mental State Examinations (MMSE) scores obtained more than 1 year apart from our memory clinic. Mean ± SD follow-up time was 3 ± 1 years, and patients had a median of 4 MMSE scores (range 2–17). We used linear mixed models with sex and age as covariates to investigate whether MBs influenced the rate of cognitive decline.

Results: Mean age was 68 ± 9 years, 109 (49%) patients were female, and the baseline MMSE score was 22 ± 4. There were 39 patients (18%) with MBs (median 2, range 1–27) and 182 without. Linear mixed models showed that overall patients declined 2 MMSE points per year. We found no association of the presence of MBs with baseline MMSE or change in MMSE. Adjustment for atrophy, white matter hyperintensities, lacunes, and vascular risk factors did not change the results nor did stratification for MB location, *APOE* ε4 carriership, or age at onset (≤65 years vs >65 years). Repeating the analyses with number of MBs as predictor rendered similar results.

Conclusion: MBs did not influence the rate of cognitive decline in patients with AD. The formerly reported increased risk of mortality in patients with MBs seems not to be attributable to a steeper rate of decline per se but might be due to vascular events, including (hemorrhagic) stroke. ***Neurology***® **2012;79:763–769**

GLOSSARY

Aβ 1–42 = Amyloid-β 1–42; **AD** = Alzheimer disease; **ARIA** = amyloid-related imaging abnormalities; **CAA** = cerebral amyloid angiopathy; **CTA** = cortical temporal lobe; **GRE** = gradient echo; **MB** = microbleed; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MTA** = medial temporal lobe atrophy; **Ptau-181** = tau phosphorylated at threonine-181.

Microbleeds (MBs) are small rounded regions of hypointensities on gradient echo (GRE) T2*-weighted MRI scans, which frequently occur in patients with Alzheimer disease (AD).[1–4] Histologically, MBs represent hemosiderin, probably from leakage through cerebral small vessels, contained within surrounding macrophages in the brain parenchyma.[5] In the setting of AD, lobar MBs in particular are believed to arise from leakage from fragile amyloid-laden vessel walls, defined as cerebral amyloid angiopathy (CAA).[6] The relationship between MBs or CAA and cognition in AD is unclear. Cross-sectionally, some studies found that AD patients with CAA or MBs are more severely cognitively impaired,[7,8] whereas others found no such relationship.[2,3,6,9] Several cross-sectional studies have reported a relationship between MBs and cognition in elderly individuals with or without increased vascular risk and in patients with small and large vessel disease.[1,10–16] Previous studies have shown that patients with MBs have a higher risk of mortality.[17,18] It is not known, however, whether patients with AD with MBs are prone to a more rapid rate of cognitive decline. In the present cohort study, we hypothesized that the presence of

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MBs reflects a heavier burden of pathology in AD, resulting in a steeper rate of cognitive decline. The aim of this study was to assess the predictive value of baseline MBs on cognitive decline over time in patients with AD.

METHODS **Patients, design, and setting.** In this cohort study, we included consecutive patients with AD who presented between 2000 and 2008 at the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center, with baseline MRI with GRE sequence on 1.0- or 1.5-T machine and a minimum duration of follow-up of 1 year. At baseline, all patients underwent a standardized dementia assessment including medical history, informant-based history, physical and neurologic examination, laboratory tests, neuropsychological testing, EEG, and MRI of the brain. Furthermore, we obtained information on smoking habits, current use of Alzheimer medication or antithrombotic drugs and medical history. Hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction were defined based on self-reported medical history and medication use. Diagnoses of probable AD were made in a multidisciplinary consensus meeting according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria.[19] None of the patients had symptomatic brain hemorrhage. The level of education was classified using the 7-point rating scale of Verhage ranging from 1 (low, elementary school not completed) to 7 (high, university). Autopsy was available for 5 patients (2 with MBs and 3 without MBs). The diagnosis of AD was confirmed in all patients. In 1 patient (no MBs), significant coexistent vascular pathology was mentioned.

We followed patients clinically, with (semi-)annual assessment of their general level of cognitive functioning. The outcome measure was the Mini-Mental State Examination (MMSE) score.[20] To be included in this study, patients had to have a minimum of 2 MMSE scores at least 1 year apart. The resulting dataset included 1,021 MMSE scores from 221 patients. Follow-up time varied between 1 and 7 years (mean ± SD 3 ± 1 years), and patients had a median of 4 MMSE scores (range 2–17) (table).

Standard protocol approvals, registrations, and patient consents. The study was approved by the local medical ethics committee. All patients gave written informed consent for their clinical data to be used for research purposes.

MRI. Baseline MRI was performed on a 1.0-Tesla machine (n = 179; Magnetom Impact Expert; Siemens AG, Erlangen, Germany) or a 1.5-T machine (n = 42; Sonata Syngo; Siemens AG). The scan protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and GRE images and has been described previously.[1,21] Scan parameters for the axial GRE images used for MB detection were as follows: impact, 19 slices; field of view, 250 mm; matrix, 256 × 256; slice thickness, 5 mm; interslice gap, 1 mm; repetition time, 800 msec; echo time, 22–25 msec; flip angle, 20°. Scan parameters for Sonata were as follows: 21 slices; field of view, 250 mm; slice thickness, 5 mm; interslice gap, 1.5 mm; repetition time, 415 msec; echo time; 25 msec; flip angle, 15°.

MRI scan rating was performed blinded to clinical data. MBs were defined as rounded hypointense homogeneous foci measuring up to 10 mm in the brain parenchyma on GRE images. Lesions in sulci possibly representing flow voids from pial vessels and symmetric lesions in the basal ganglia, supposedly representing iron or calcium deposits, were not taken into account. Hypointensities inside infarcts were not counted as MBs but were regarded as being probable hemorrhagic transformations. Cavernous angiomas were not taken into account. We counted MBs in 4 lobar regions (frontal, parietal, temporal, and occipital) and in 2 nonlobar regions (basal ganglia including thalamus and infratentorial). The main determinant was the presence of at least one MB. In additional analyses, the number of MBs and MB by location were used as determinants.

We performed visual rating of medial temporal lobe atrophy (MTA) on coronal T1-weighted images according to the 5-point (0–4) Scheltens scale.[22] Global cortical atrophy (GCA) (range 0–3)[23] and white matter hyperintensity (WMH) severity (Fazekas, range 0–3)[24] were rated visually on axial FLAIR images; the highest scores represent maximal pathology. We counted lacunar

Table Baseline demographic and clinical characteristics

	No microbleeds	≥1 microbleeds
No. patients	182	39
Female sex, n (%)	94 (52)	15 (39)
Age, y, mean (SD)	67 (9)	71 (8)[a]
Education, median (range)[b,g]	5 (2–7)	5 (2–7)
APOE ε4 carriers, n (%)[c]	111 (71)	20 (69)
MMSE score at baseline, mean (SD)	22 (4)	22 (4)
Follow-up time, y, mean (SD)	3 (1)	3 (1)
No. of MMSE scores, median (range)	4 (2–17)	4 (2–10)
Mortality, n (%)	24 (13)	8 (21)
Smoking, n (%)[d]	26 (16)	3 (8)
Hypertension, n (%)[b]	48 (27)	20 (51)[a]
Diabetes mellitus, n (%)[b]	12 (7)	3 (8)
Hypercholesterolemia, n (%)[b]	28 (16)	9 (23)
Myocardial infarction, n (%)[b]	6 (3)	3 (8)
Use of antithrombotic drugs, n (%)[b]	32 (18)	13 (33)[a]
Use of Alzheimer medication, n (%)[b]	13 (7)	2 (5)
CSF amyloid-β 1–42, pg/mL[e,f]	459 (166)	406 (153)[a]
Total tau, pg/mL[e,f]	639 (399)	739 (497)
Tau phosphorylized at threonine 181, pg/mL[e,f]	87 (34)	94 (44)
Microbleeds, median (range)		2 (1–27)[a]
MTA, mean (SD)[f]	1.4 (0.9)	1.9 (1.0)[a]
GCA, mean (SD)[f]	1 (1)	1 (1)
WMHs, mean (SD)[e]	0.8 (0.8)	1.5 (1.0)[a]
Lacunes, mean (SD)[d]	0 (0)	0 (1)

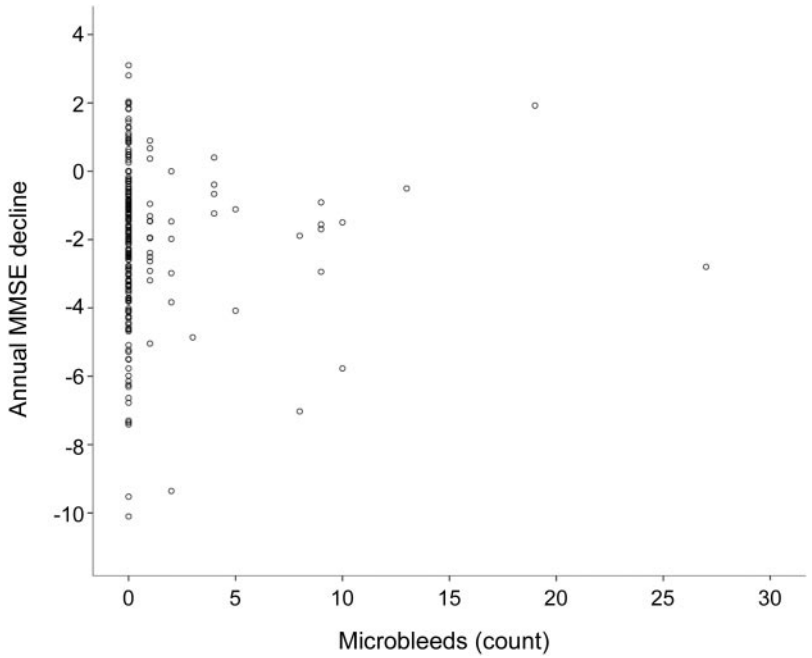
Abbreviations: GCA = global cortical atrophy; MMSE = Mini-Mental State Examination; MTA = medial temporal lobe atrophy; ptau = tau phosphorylized at threonine 181; WMH = white matter hyperintensity.
[a] $p < 0.05$.
[b] Data available for 219 patients.
[c] Data available for 186 patients.
[d] Data available for 196 patients.
[e] Data available for 158 patients.
[f] Analyses were performed with nonparametric Mann-Whitney *U* tests.
[g] Education was rated using Verhage code, ranging from 1 (elementary school not finished) to 7 (university).

infarcts, defined as well-demarcated lesions from 3 to 15 mm, with a CSF-like signal on all sequences.

***APOE* and CSF biomarkers.** DNA was isolated from 10 mL of EDTA blood. The *APOE* genotype was determined with the Light Cycler *APOE* mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). The *APOE* genotype was available for 186 patients. CSF biomarkers were assessed as markers of Alzheimer neuropathology. CSF was obtained by a lumbar puncture. Amyloid-β 1–42 (Aβ42), total tau, and tau phosphorylated at threonine-181 (Ptau-181) were measured by sandwich ELISA (Innotest β-amyloid$_{(1-42)}$, Innotest hTau Ag, and Innotest Phospho tau$_{(181P)}$; Innogenetics, Gent, Belgium).[25] CSF was available for 158 patients.

Statistical analysis. We used SPSS 15.0 to perform statistical analyses. Baseline differences between groups were studied using Student *t* test, Mann-Whitney *U* test, or χ^2 test where applicable. We used linear mixed models to assess associations between the presence of MBs and the rate of cognitive decline as measured by MMSE. This approach has increased statistical power because it accounts for within-person correlations over time, allows different numbers of assessments, and accounts for varying time intervals between assessments. A random intercept and a random slope with time (in years) were assumed, i.e., baseline MMSE (main effect of MBs) and change in MMSE over time (interaction effect of MBs × time) were allowed to vary between patients. The first model included terms for the presence of MBs, time, and the interaction between presence of MBs and time with sex and age as covariates and MMSE score as the dependent variable. Secondly, we used a model with additional adjustment for MTA, GCA, WMHs, and the presence of lacunes. A third model also adjusted for the following potential confounders: smoking, hypertension, diabetes, hypercholesterolemia, myocardial infarction, and use of antithrombotic drugs or Alzheimer medication. Furthermore, we repeated the analyses after stratification according to age at onset (≤65 years vs >65 years) and according to *APOE*- ε4 carriership (noncarriers vs carriers). The same models were run with a term for the number instead of the presence of MBs. Finally, we ran the models again to assess the influence of the location of MBs on the rate of MMSE score change over time in 2 ways: first with a categorical variable based on the presumed underlying etiology, defined as 1) no MBs, 2) strictly nonlobar MBs, 3) strictly lobar MBs, and 4) both lobar and nonlobar MBs and second with a categorical variable based on laterality defined as 1) no MBs, 2) left-sided MBs, 3) right-sided MBs, and 4) bilateral MBs.

Figure 1 **Number of microbleeds (MBs) by Mini-Mental State Examination (MMSE) score change per annum**

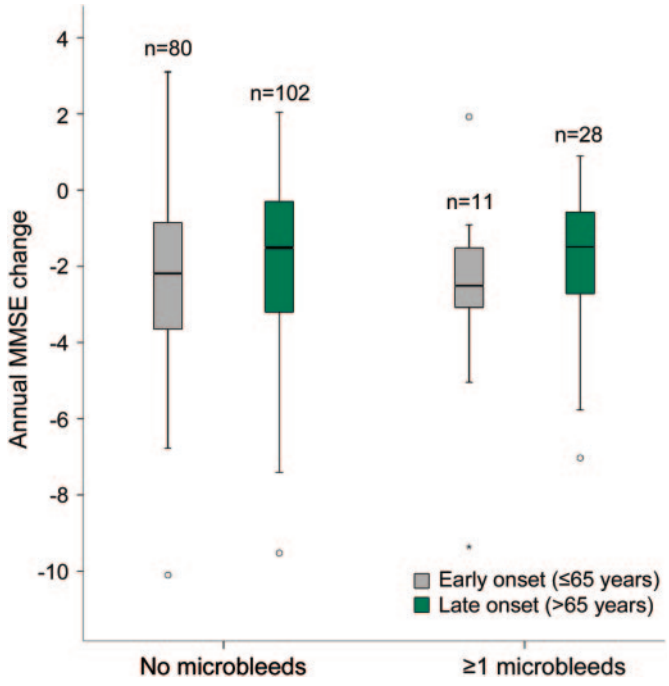


MMSE score change per annum was calculated as last MMSE score minus first MMSE score, divided by follow-up time in years. Note that for the statistical analysis linear mixed models were used, which showed no association between MBs and rate of cognitive decline.

RESULTS Demographic and clinical characteristics of the study sample are presented in the table. Of the patients, 18% had one or more MBs, and 82% had no MBs. Patients with MBs were older than patients without MBs. Groups did not differ in sex, education, *APOE* ε4 carriership, follow-up time, or number of follow-ups. Patients with MBs more often died within the study period, although this difference did not reach significance. Patients with MBs more often had a history of hypertension, and they more often used antithrombotic drugs, but there were no differences in other vascular risk factors. Furthermore, patients with MBs had lower CSF levels of Aβ42, but there were no differences in tau or Ptau-181. Relative to normal values, both groups showed decreased CSF levels of Aβ42 and increased CSF levels of total tau and Ptau-181 (normal values: Aβ42 ≥550, total tau ≤375, and Ptau-181 ≤52).[25] Patients with MBs had more MTA and WMHs than patients without MBs. We found no differences between groups for GCA or number of lacunes.

Linear mixed models with random intercept and slope showed that across groups, patients declined 2 MMSE score points per year (β [SE] = −2.10 [0.31], p = 0.00). No association of MB presence with baseline MMSE (β [SE] = 0.26 [0.72], p = 0.72) or rate of cognitive decline (β [SE] = 0.01 [0.34], p = 0.97) was found (figure 1). Adjustment for MTA, GCA, WMHs, and number of lacunes did not change the results (baseline MMSE score: β [SE] = 0.34 [0.76], p = 0.65); rate of decline: β [SE] = −0.09 ([0.34], p = 0.79), nor did further adjustment for smoking, hypertension, diabetes, hypercholesterolemia, myocardial infarction, or use of antithrombotic drugs or Alzheimer medication. In addition, stratification according to age at onset (figure 2) and *APOE* ε4 carriership (figure 3) did not reveal any associations between MBs and cognition. We repeated all analyses with MBs as a continuous measure to study the associations with the number, rather than the presence, of MBs, which did not reveal any associations with baseline MMSE score or rate of cognitive decline either. Furthermore, restricting the

Figure 2 Annual Mini-Mental State Examination (MMSE) score for patients with and without microbleeds (MBs), stratified according to age at onset



Annual MMSE score change was calculated as last MMSE score minus first MMSE score, divided by follow-up time in years. Note that for the statistical analysis linear mixed models were used, which showed no association between MBs and rate of cognitive decline for either patients with early or late disease onset (≤65 years or >65 years).

sample to patients with MBs only showed no associations of number of MBs with baseline MMSE (β [SE] = −0.15 [0.13], p = 0.23) or rate of cognitive decline (β [SE] = 0.00 [0.05], p = 0.98). When the location of the MBs (no MBs, strictly nonlobar MBs, strictly lobar MBs, or both lobar and nonlobar MBs) was taken into account, we observed no association of location of MBs with baseline MMSE or rate of cognitive decline (all p values >0.05) (figure 4). Similarly, location of MBs in terms of laterality (no MBs, left-sided MBs, right-sided MBs, or bilateral MBs) did not reveal any associations (data not shown).

DISCUSSION The main finding of this longitudinal study is that the presence and number of MBs are not associated with rate of cognitive decline in AD. Neither stratification for age at onset or *APOE* genotype, nor taking into account MB location (deep vs lobar or left hemisphere vs right hemisphere), nor restricting the analysis to patients with MBs only revealed any significant relation between MBs and rate of cognitive decline in this clinical sample of patients with AD.

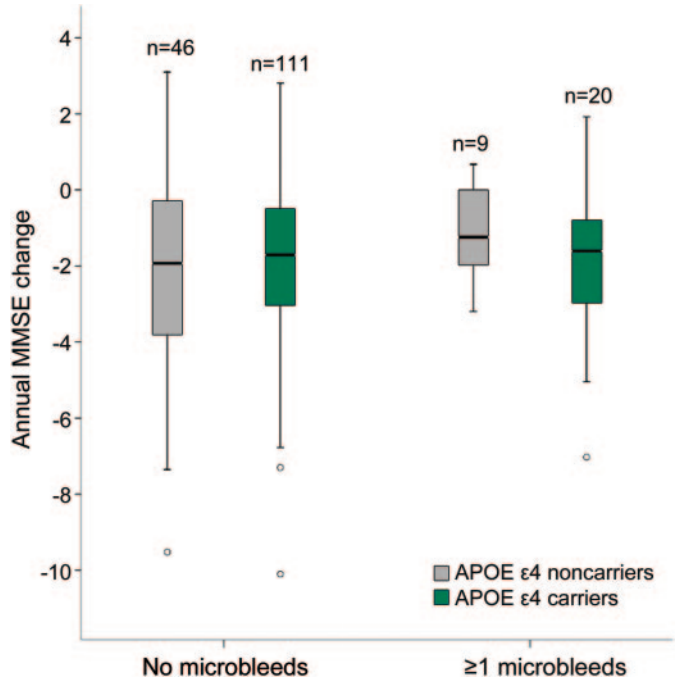
There are 2 former longitudinal studies that have looked into the relationship between MBs and rate of cognitive decline in mild cognitive impairment (MCI) and are in line with our findings. One study found no difference in MBs between patients with stable and progressive MCI after 1 year.[26] The other study found that the presence of MBs predicts conversion from MCI to dementia, but the significance of this effect was lost after adjustment for age.[27]

Previous studies have suggested that the presence of one or a few MBs does no real harm but having multiple MBs is indicative of a more malignant outcome. Despite a modestly, although nonsignificantly, increased mortality rate, we were not able to demonstrate an association between the presence or number of MBs and rate of cognitive decline. In AD, it seems that downstream phenomena such as loss of synapses and neurodegeneration are largely responsible for cognitive decline. Our results suggest that MBs do not affect these downstream pathologic Alzheimer processes. Two previous studies showed that patients with multiple MBs have a higher risk of mortality.[17,18] Our current results support the notion that the increased risk of mortality in patients with AD with MBs is not related to the Alzheimer process itself, but rather to vascular events, including (hemorrhagic) stroke.

Variability in rate of decline on MMSE in our sample of patients with AD was large. The determinants of the rate of decline in AD are largely unknown, because we are presently unable to predict which patients will show faster progression than others. The current study shows that MBs are not an important determinant of rate of decline in AD. We cannot exclude the possibility that MBs have a subtle effect on rate of cognitive decline; however, in the context of AD, the clinical significance of such a subtle effect would be limited. Still, MBs may influence change in cognition in other populations, such as populations without dementia. Cross-sectionally, several studies have reported a relationship between MBs and cognition in elderly individuals with or without increased vascular risk[10–12,14] and in patients with small- and large-vessel disease.[13,15] Whether MBs also predict change in cognitive performance over time in these populations remains to be determined.

We took into account location of MBs in a number of analyses, but we found no relationship between MBs in a specific location (be it lobar vs nonlobar or left vs right hemisphere) and rate of cognitive decline. It is still conceivable that the localization of MBs could be relevant, but that such an effect is not reflected in the overall MMSE score. Cross-sectional studies have suggested that MBs are largely related to tests of mental speed and executive functioning.[10,13–15] Whether or not the exact location of MBs is relevant in terms of reflecting focal damage

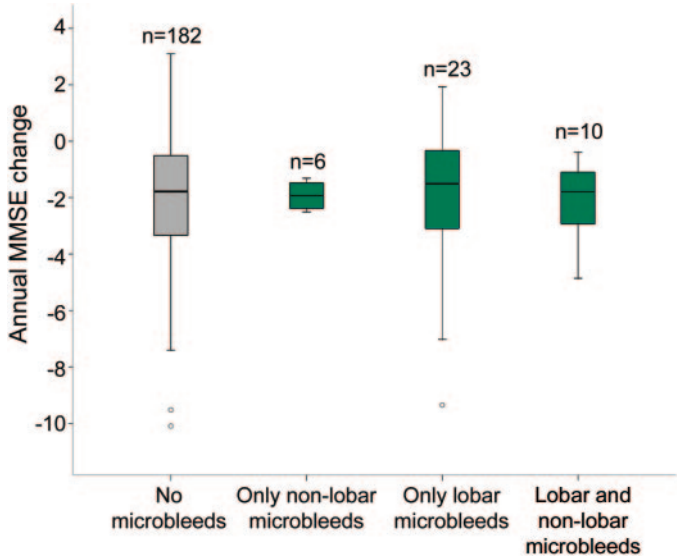
Figure 3 Annual Mini-Mental State Examination (MMSE) score change for patients with and without microbleeds (MBs), stratified according to *APOE* ε4 genotype



Annual MMSE score change was calculated as last MMSE score minus first MMSE score, divided by follow-up time in years. Note that for the statistical analysis linear mixed models were used, which showed no association between MBs and rate of cognitive decline for either *APOE* ε4 carriers or noncarriers.

remains to be demonstrated, however. Alternatively and perhaps more likely is the view that MBs are a tip of the iceberg phenomenon, reflecting widespread underlying vasculopathy.

Figure 4 Annual Mini-Mental State Examination (MMSE) score change according to the presence and location of microbleeds (MBs)



Linear mixed models showed no association between the location of MBs and the rate of cognitive decline.

The current study was designed to relate baseline MRI scans to changes in cognitive functioning. Repeated MRI scans would have allowed us to relate the incidence of new MBs to rate of cognitive decline, but this was beyond the scope of the current study. In a former study, we have shown that incident MBs occurred in 12% of patients over a 2-year period and were not related to change in cognition.[28] Similarly, others have shown that the occurrence of new MBs did not predict clinical decline in patients with intracerebral hemorrhage.[16]

Among the strengths of the current study is the large sample size of patients who were all screened using the same, careful diagnostic workup. MRI protocols were kept constant over the whole inclusion period. Although misdiagnoses cannot be completely ruled out, all diagnoses were made according to clinical criteria and patients were followed clinically. Moreover, in the majority of patients, CSF biomarkers were available to substantiate the clinical diagnosis. Another strength is the use of linear mixed models for statistical analyses. These models take into account all available data points, allowing patients to have variable numbers of follow-up measurements. In this way, patients with only 2 available MMSE scores could also be included in the study, because the statistical model appropriately takes into account the fact that the estimate of cognitive decline is less precise in these patients. A potential limitation is the relatively few patients with AD with MBs, because despite the large sample size of 221 patients with clinical follow-up, only 39 had MBs. Still, this number is in agreement with the previously reported prevalence of MBs in AD and the large group of patients without any MBs adds power to the statistical analyses. A second limitation is that although information on the use of Alzheimer medication and other types of medication at baseline was available, use of medication in the course of the disease was not recorded. Nonetheless, although the use of cholinesterase inhibitors and memantine may have influenced the rate of cognitive decline, we do not suspect that this effect would be different for patients with MBs than for those without MBs. Third, our outcome measure was the MMSE score, a crude measure of cognitive decline, which does not capture all aspects of disease severity. Still, the MMSE is a generally accepted and widely used test for the evaluation of cognition in elderly patients. A future study should investigate the impact of MBs on the decline of specific cognitive domains and on the relationships between MBs and neuropsychiatry symptoms in populations without dementia also, in which the subtle effects of MBs may still be discerned.

Recently, the interest in the clinical consequence of MBs has risen, because amyloid-related imaging abnormalities (ARIA) including cerebral MBs have occurred in patients participating in clinical trials with therapeutic agents to lower the amyloid-β burden in AD.[29] In this context, our finding of a lack of association between MBs and the rate of cognitive decline may be of importance. If the rate of cognitive decline, often a primary outcome measure in clinical trials, is not influenced by the presence and number of MBs, excluding patients with MBs may not be necessary. However, it should be noted that the prognosis of ARIA-hemosiderin deposition may be different from that of spontaneously occurring MBs. Therefore, further research is needed regarding the risk of accelerated cognitive decline in patients with ARIA-hemosiderin deposition.

AUTHOR CONTRIBUTIONS

A.E. van der Vlies, J.D.C. Goos, P. Scheltens, and W.M. van der Flier conceived the study. J.D.C. Goos and F. Barkhof performed the MRI ratings. Statistical analyses were performed by A.E. van der Vlies and W.M. van der Flier. A.E. van der Vlies drafted the manuscript, and all authors revised it.

DISCLOSURE

A.E. van der Vlies and J.D.C. Goos report no disclosures. F. Barkhof serves/has served on the advisory boards of Bayer-Schering Pharma, sanofi-aventis, Biogen Idec, UCB, Merck-Serono, Novartis, and Roche. He received funding from the Dutch MS Society and has been a speaker at symposia organized by the Serono Symposia Foundation. For all his activities he receives no personal compensation. P. Scheltens serves/has served on the advisory boards of Genentech, Novartis, Roche, Danone, Nutricia, Baxter, and Lundbeck. He has been a speaker at symposia organized by Lundbeck, Merz, Danone, Novartis, Roche, and Genentech. For all his activities he receives no personal compensation. He is a member of the scientific advisory board of the EU Joint Programming Initiative and the French National Plan Alzheimer. The Alzheimer Center receives unrestricted funding from various sources through the VU University Medical Center Fonds. W.M. van der Flier reports no disclosures. **Go to Neurology.org for full disclosures.**

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