

Progression of Mild Cognitive Impairment to Dementia Contribution of Cerebrovascular Disease Compared With Medial Temporal Lobe Atrophy

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Background and Purpose—We sought to determine the predictive value of magnetic resonance imaging measures of vascular disease (white matter hyperintensities [WMHs], lacunes, microbleeds, and infarcts) compared with atrophy on the progression of mild cognitive impairment to dementia.

Methods—We included 152 consecutive patients with mild cognitive impairment. Baseline magnetic resonance imaging was used to determine the presence of medial temporal lobe atrophy and vascular disease (presence of lacunes, microbleeds, and infarcts was determined, and WMHs were rated on a semiquantitative scale). Patients were followed up for 2 ± 1 years.

Results—Seventy-two (47%) patients progressed to dementia during follow-up. Of these, 56 (37%) patients were diagnosed with Alzheimer's disease, and 16 (10%) patients were diagnosed with a non-Alzheimer dementia (including vascular dementia, frontotemporal lobar degeneration, and Parkinson dementia). Converters were older and had a lower Mini-Mental State Examination score at baseline. On baseline magnetic resonance imaging, patients who progressed to a non-Alzheimer dementia showed more severe WMHs and had a higher prevalence of lacunes in the basal ganglia and microbleeds compared with nonconverters. Cox proportional-hazard models showed that, adjusted for age and sex, baseline medial temporal lobe atrophy (hazard ratio=2.9; 95% CI, 1.7 to 5.3), but not vascular disease, was associated with progression to Alzheimer's disease. By contrast, deep WMHs (hazard ratio=5.7; 95% CI, 1.2 to 26.7) and periventricular hyperintensities (hazard ratio=6.5; 95% CI, 1.4 to 29.8) predicted progression to non-Alzheimer dementia. Furthermore, microbleeds (hazard ratio=2.6; 95% CI, 0.9 to 7.5) yielded a >2-fold increased, though nonsignificant, risk of non-Alzheimer dementia.

Conclusion—Medial temporal lobe atrophy and markers of cerebrovascular disease predict the development of different types of dementia in mild cognitive impairment patients. (*Stroke*. 2009;40:1269-1274.)

Key Words: mild cognitive impairment ■ dementia ■ magnetic resonance imaging ■ vascular disease ■ atrophy

Mild cognitive impairment (MCI) is characterized by mild cognitive deficits not sufficient for a diagnosis of dementia.¹ MCI patients have an increased risk of progression to dementia, mostly Alzheimer's disease (AD), although the risk of another type of dementia is known to be elevated as well.¹⁻³ Atrophy of the medial temporal lobe (MTA), including the hippocampus and entorhinal cortex, is a sensitive marker for AD. Visual assessment of MTA has been shown to be a powerful and independent predictor of progression to dementia in MCI patients.⁴⁻⁶ Additionally, global cortical atrophy has been demonstrated to be related to progression of MCI to dementia.⁷ In contrast to atrophy, the impact of cerebrovascular disease on progression to dementia is less clear.

Only a small number of longitudinal studies have examined the role of vascular disease in MCI patients, and results

have been conflicting.⁷⁻¹¹ One study found white matter hyperintensities (WMHs) to be associated with the risk of progression from normal cognitive function to MCI, but not from MCI to dementia.⁷ This is in line with another report that did not find an association between cerebrovascular disease (ie, clinical stroke, extent of WMHs, or presence of lacunes) and progression of MCI to dementia.⁹ In contrast, others did find a relation between WMHs and progression to AD in MCI patients.¹⁰ Nonetheless, this study was small ($n=27$) and used computed tomography instead of magnetic resonance imaging (MRI). More recently, a study in a large sample of MCI patients reported an association between WMHs and cognitive decline.⁸ Furthermore, the same group reported WMHs to be related to an increased risk of vascular or mixed dementia, but not of AD.¹¹ Expression of vascular

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disease other than WMHs, such as lacunes and microbleeds, was not taken into account. Little is known about the role of microbleeds and cognitive function in MCI or dementia patients, apart from 1 report that found a relation between microbleeds and cognitive impairment in subcortical vascular dementia.¹² Another study in nondemented patients with cerebrovascular disease reported a relation between microbleeds and executive dysfunction.¹³ The aim of this study was to assess the predictive value of MRI measures of both atrophy and vascular disease, including infarcts, WMHs, lacunes and microbleeds, with respect to progression of MCI to dementia.

Subjects and Methods

Patients

We consecutively recruited 152 patients with MCI from the outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre. Standardized assessment included medical history, neurologic examination, laboratory tests, neuropsychologic testing including Mini-Mental State Examination (MMSE),¹⁴ electroencephalography, and MRI of the brain. Diagnoses were made in a multidisciplinary consensus meeting according to the Petersen criteria.¹ 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.

Clinical Follow-Up

All patients were annually re-examined for possible alteration in cognitive function with a mean follow-up of 2 ± 1 years. Standardized assessment included careful history and cognitive testing. All patients in this study were re-evaluated at least once (maximum, 5). Patients with stable or improved cognitive function at follow-up were regarded as nonconverters. Patients who progressed to dementia were regarded as converters. Converters were classified in 2 clusters. One cluster included patients who progressed to AD. The other cluster consisted of patients who progressed to a non-Alzheimer dementia, including vascular dementia (VaD), frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB). To diagnose AD, we used the criteria of the National Institute on Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association.¹⁵ VaD was diagnosed by use of the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),¹⁶ FTLD was diagnosed by the Neary and Snowden criteria,¹⁷ and DLB was diagnosed by the McKeith criteria.¹⁸

MRI Protocol

At baseline, MRI was performed on a 1.0-T machine (Magnetom Impact Expert Siemens AG, Erlangen, Germany) according to a standard protocol, including coronal T1-weighted 3D magnetization prepared rapid acquisition gradient echo (168 slices; field of view=250 mm; matrix=256×256; slice thickness=1.5 mm; echo time=7 ms; repetition time=15 ms; inversion time=300 ms; flip angle=5°); axial fluid-attenuated inversion recovery (FLAIR; 17 slices; field of view=250 mm; matrix=256×256; slice thickness=5 mm; interslice gap=1.5 mm; echo time=105 ms; repetition time=9000 ms; inversion time=2200 ms; flip angle=180°), and axial T2*-weighted gradient echo sequences (19 slices; field of view=250 mm; matrix=256×256; slice thickness=5 mm; interslice gap=1.5 mm; echo time=22 ms; repetition time=800 ms; flip angle=20°).

Image Assessment

Baseline MRI was used to determine the presence of atrophy and vascular disease. Visual rating of MTA was performed on coronal T1-weighted images according to the 5-point (0–4) Scheltens scale

from the average score of the left and right sides.¹⁹ Global cortical atrophy was assessed visually on axial FLAIR images (possible range of scores 0 to 3).²⁰ The degree of WMH severity was rated on axial FLAIR images on a semiquantitative scale.²¹ Periventricular and deep WMHs (DWMHs) were rated separately, the rating for each score being based on both size and number of lesions in different anatomic regions. Periventricular hyperintensities (PVHs) were defined as lesions adjacent to the lateral ventricles or the occipital or frontal horns resulting in a score ranging from 0 to 6. DWMHs were defined as lesions located in the frontal, parietal, occipital, and temporal deep white matter with a maximum score of 6 for each region to give a total score ranging from 0 to 24. A total WMH score was composed by summing the PVH and DWMH scores, ranging from 0 to 30. Ratings of basal ganglia and infratentorial hyperintensities were not included in the present study. Lacunes were defined as T1-hypointense and T2-hyperintense cerebrospinal fluid–like lesions surrounded by white matter or subcortical gray matter with a minimum diameter of 3 mm, not located in areas with a high prevalence of widened perivascular spaces (vertex, anterior commissure). Next to an overall count of lacunes, the presence of ≥ 1 lacune in the basal ganglia was determined. Microbleeds were defined as strongly hypointense, mostly round lesions on the axial FLASH 2D images with a diameter between 2 and 10 mm. Symmetrical hypointensities in the globi pallidi, most likely to be calcification or iron deposition, and flow void artifacts of the pial blood vessels were disregarded. The presence of infarcts was determined from the different MRI sequences.

Statistical Analysis

Statistical analysis was performed with SPSS 14.0 (SPSS Inc). For analyzing purposes, MRI measures were dichotomized, with the median score of the total population for the WMH measurements. This resulted in the following categories: severe MTA: <1.5 absent, ≥ 1.5 present; severe PVH: <3 absent, ≥ 3 present; severe DWMH: <4 absent, ≥ 4 present; severe WMH: <6 absent, ≥ 6 present; presence of ≥ 1 lacune, presence of ≥ 1 microbleed, presence of ≥ 1 infarct. Group comparisons were performed with χ^2 tests for dichotomous variables and independent samples *t* tests for continuous data. Next, Cox proportional-hazards models, which account for varying follow-up times, were used to investigate the risk of progression to dementia depending on the various dichotomized MRI measures. The analysis was performed twice, first using progression to AD as the outcome measure with the nonconverters as a reference group. Subsequently, progression to a non-Alzheimer dementia was analyzed as a second outcome measure, with the nonconverters again as a reference group. Data are presented as hazard ratio (HR) and accompanying 95% CI. The first model shows the crude risk estimates. In the second model, we adjusted for age and sex. Significance was set at $P < 0.05$.

Results

Of the total 152 MCI patients, 72 (47%) progressed to dementia during follow-up. Fifty-six patients (37%) were diagnosed with AD, and 16 patients (10%) were diagnosed with a non-Alzheimer dementia (VaD $n=7$, FTLD $n=5$, DLB $n=2$, Parkinson dementia $n=1$, alcohol dementia $n=1$). Converters had a slightly longer follow-up duration and were older, were more likely to be female, and had a lower MMSE at baseline (Table 1).

Baseline MRI measures are presented in Table 2. Both patients who progressed to AD and those who progressed to a non-Alzheimer dementia showed more MTA and more cortical atrophy than did nonconverters. Measures of vascular disease were more prevalent among patients who progressed to non-Alzheimer dementia compared with nonconverters: the severity of WMHs (both PVHs and DWMHs) was higher in patients who progressed to a non-Alzheimer dementia

Table 1. Baseline Characteristics

	Nonconverters	Converters	AD	Non-Alzheimer Dementia
Patients, n (%)	80 (53%)	72 (47%)	56 (37%)	16 (10%)
Follow-up duration, y	1.8 (1.1)	2.2 (1.3)†	2.2 (1.3)	2.2 (1.4)
Age, y	68 (9)	72 (7)‡	72 (7)†	75 (6)‡
Women, n (%)	31 (39%)	40 (56%)†	33 (59%)†	7 (44%)
MMSE at baseline	27 (2)	26 (2)‡	26 (2)‡	27 (2)
MMSE at follow-up*	27 (2)	20 (5)§	20 (5)§	21 (5)‡

Data are presented as mean (SD) or n (%). Comparison of data by χ^2 or *t* test when appropriate, with the nonconverters as the reference group.

*Available for 113 patients.

Compared with nonconverters: †*P*<0.05; ‡*P*<0.01; §*P*<0.001.

compared with nonconverters. In addition, these patients more often had lacunes in the basal ganglia and microbleeds.

Cox proportional-hazard models showed that, adjusted for age and sex, baseline MTA predicted progression to AD (HR=2.9; 95% CI, 1.7 to 5.3; Table 3). None of the measures of vascular disease predicted progression to AD. A different picture emerged for progression to non-Alzheimer dementia. Adjusted for age and sex, severe WMHs (HR=5.8, 95% CI, 1.2 to 26.6) were strongly associated with progression to non-Alzheimer dementia. This association was attributable to both PVHs (HR=6.5; 95% CI, 1.4 to 29.8; eg, see Figure 1) and DWMHs (HR=5.7, 1.2 to 26.7), with the highest risk for PVHs. Furthermore, the presence of microbleeds conferred an almost 3-fold, though still nonsignificant, increased risk of progression to non-Alzheimer dementia (HR=2.6; 95% CI, 0.9 to 7.5). The same was seen for the presence of lacunes in the basal ganglia, which showed a >2-fold, though nonsignificant, predictive value on progression to non-Alzheimer dementia (HR=2.4; 95% CI, 0.8 to 7.5). These results remained essentially unchanged after additional adjustment for MTA or MMSE (data not shown). Moreover, MTA showed a 2-fold, though nonsignificant increased risk for progression to non-Alzheimer dementia (HR=2.5; 95% CI, 0.8 to 7.2; eg, see Figure 2).

Discussion

We showed that in MCI patients, MTA and markers of cerebrovascular disease predicted progression to different

types of dementia. MTA was a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease was independently associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.

The role of atrophy in progression to dementia has been shown before. Earlier reports already noted visual assessment of MTA as good predictor of progression of MCI to dementia.⁴⁻⁶ MTA has been shown to be present not only in patients with AD but also in other dementias (like VaD and DLB).²²⁻²⁴ This is in line with our noticeable, though nonsignificant, >2-fold, increased risk of MTA for progression to a non-Alzheimer dementia.

There has been growing interest lately in the possible influence of vascular factors in the development of AD. Vascular risk factors, like hypertension and diabetes, have been associated with an elevated risk of AD, and AD patients have been reported to show more vascular abnormalities on MRI than controls.²⁵⁻²⁹ Contrary to our expectation, we did not find any relation between the presence of cerebrovascular disease on baseline MRI and progression to AD. With respect to WMHs, this is in line with some^{9,11} but not all¹⁰ previous reports. However, the latter study was small and used computed tomography instead of MRI.¹⁰ Although we found no influence of WMHs on progression from MCI to AD, progression to non-Alzheimer dementia was strongly associated with both PVHs and DWMHs, with the highest risk attributable to PVHs. These findings confirm the recently

Table 2. Baseline MRI Characteristics

	Nonconverters	Converters	AD	Non-Alzheimer Dementia
MTA	0.7 (0.8)	1.4 (0.9)§	1.4 (1.0)§	1.2 (0.8)‡
Cortical atrophy	0.6 (0.7)	1.0 (0.8)‡	1.0 (0.7)‡	1.2 (0.9)‡
PVHs	2.3 (1.7)	2.9 (1.6)	2.6 (1.5)	3.8 (1.5)‡
DWMHs	4.9 (5.4)	5.4 (5.2)	4.4 (4.6)	8.9 (5.6)‡
Total WMHs	7.1 (6.9)	8.3 (6.5)	6.9 (5.9)	12.7 (6.9)‡
Presence of ≥1 lacune, n (%)	15 (19%)	15 (21%)	10 (18%)	5 (31%)
Presence of ≥1 lacune BG, n (%)	9 (11%)	13 (18%)	8 (14%)	5 (31%)†
Presence of ≥1 MB, n (%)*	11 (15%)	10 (16%)	4 (9%)	6 (38%)†
Presence of ≥1 infarct, n (%)	5 (6%)	4 (6%)	3 (5%)	1 (6%)

MB indicates microbleed; BG, basal ganglia. Data are presented as mean (SD) unless otherwise specified. Comparison of data by χ^2 or *t* test when appropriate with the nonconverters as the reference group.

*Missing nonconverters n=5, AD n=9.

Compared with nonconverters: †*P*<0.05; ‡*P*<0.01; §*P*<0.001.

Table 3. Cox Regression Analysis

	AD		Non-Alzheimer Dementia	
	Model 1	Model 2	Model 1	Model 2
MTA	2.9 (1.7–5.0)	2.9 (1.7–5.3)	2.9 (1.1–7.9)	2.5 (0.8–7.2)
GCA	1.6 (0.8–3.1)	1.4 (0.7–2.7)	2.4 (0.8–7.0)	2.2 (0.7–7.0)
PVHs	1.3 (0.7–2.2)	1.1 (0.7–2.0)	7.3 (1.7–32.4)	6.5 (1.4–29.8)
DWMHs	1.4 (0.8–2.4)	1.3 (0.8–2.3)	5.7 (1.3–25.5)	5.7 (1.2–26.7)
Total WMHs	1.3 (0.8–2.2)	1.2 (0.7–2.2)	6.0 (1.3–26.8)	5.8 (1.2–26.6)
Lacunes	1.2 (0.6–2.4)	1.1 (0.5–2.2)	2.3 (0.8–6.8)	2.1 (0.7–6.4)
Lacunes basal ganglia	1.4 (0.7–3.0)	1.2 (0.6–2.6)	2.7 (0.9–8.1)	2.4 (0.8–7.5)
Microbleeds	0.7 (0.3–2.0)	0.8 (0.2–2.2)	2.5 (0.9–7.2)	2.6 (0.9–7.5)
Infarcts	0.8 (0.3–2.6)	1.1 (0.3–3.8)	0.8 (0.1–6.6)	1.4 (0.2–12.1)

MTA indicates medial temporal lobe atrophy; GCA, global cortical atrophy. Data are presented as HR (95% CI). Cox regression analysis compared progression to AD and non-Alzheimer dementia with nonconverters. The first model was unadjusted; the second model was adjusted for age and sex.

reported predictive value of DWMHs and especially PVHs for vascular or mixed dementia.¹¹ Others did not find a predictive value of WMHs for progression to non-Alzheimer dementia.^{7,9} Nonetheless, in both of these last-mentioned studies, the number of patients was small (3 and 7 patients, respectively). We had a sample of 16 patients who progressed to a non-Alzheimer dementia. Of these, the largest subgroup consisted of VaD. Still, the effect did not seem attributable to

this group alone, because in patients with Parkinson dementia, DLB, and alcohol dementia especially, we observed vascular disease as well. We are not sure how to interpret this finding. It is known that cerebrovascular disease can cause parkinsonism.³⁰ Alternatively, it must be noted that diagnosis was based on clinical criteria, leaving the possibility of mixed disease. Unfortunately, the sample size did not allow examination of progression to specific dementia types other than AD.

We demonstrated that the prevalence of lacunes in the basal ganglia was higher in patients who progressed to non-Alzheimer dementia compared with nonconverters. A population-based study showed that silent mostly lacunar brain infarcts were a risk factor for dementia.²⁹ Other reports in MCI patients did not find an association between lacunes and progression to dementia.^{9,31} In this study, Cox analysis of

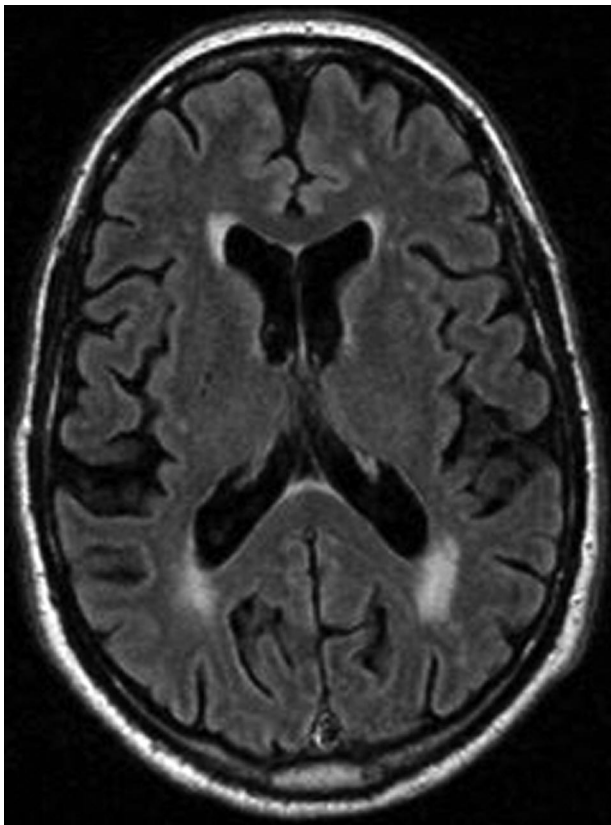


Figure 1. Axial FLAIR image of a patient diagnosed after 1 year of follow-up with DLB, showing beginning confluent WMHs mainly around the ventral and occipital horns of the lateral ventricles. Additionally, this patient showed a lacune in the nucleus caudatus and 2 microbleeds (images not shown).

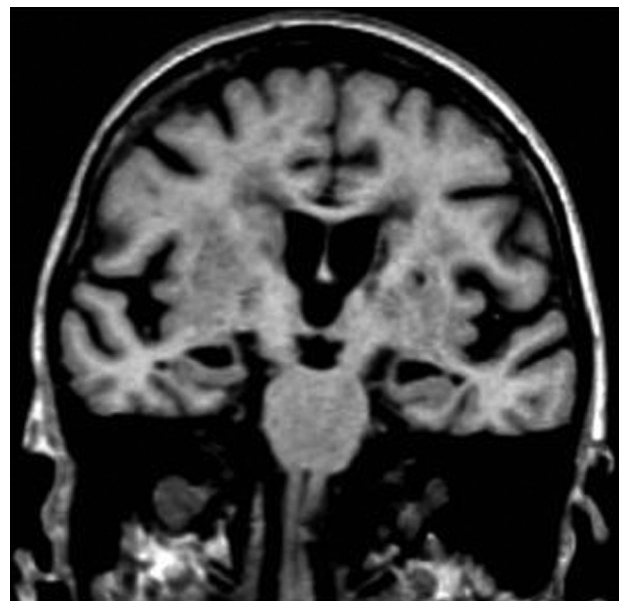


Figure 2. Coronal T1-weighted image of a patient diagnosed after 2 years of follow up with VaD, showing an MTA score of 2 on the left and the right side. In addition, this patient showed confluent WMHs, 2 lacunes (paraventricular and basal ganglia left hemisphere), and 1 microbleed (images not shown).

lacunes in the basal ganglia was, although borderline significant; suggestive of a >2-fold elevated risk of progression to a non-Alzheimer dementia. We did not find a predictive value of large-vessel infarcts on progression of MCI to dementia. Although having a (large-vessel) stroke is known to double the risk of dementia,³² in MCI patients the absence of progression related to infarcts has been reported before.⁹ A study in patients with VaD found that patients with multi-infarct or strategic infarct dementia were predominantly diagnosed directly from a cognitive normal status, whereas patients with VaD based on small-vessel disease often go through a stage of MCI.³³

Our study showed that the prevalence of microbleeds was higher in patients who progressed to a non-Alzheimer dementia compared with nonconverters. Furthermore, the presence of microbleeds showed an almost 3-fold, borderline significant risk for progression to a non-Alzheimer dementia. Little research has been performed on the role of microbleeds in MCI patients and on microbleeds in relation to cognitive dysfunction. A study in 86 patients with subcortical VaD found microbleeds to be related to all cognitive domains with the exception of language function.¹² Another study in nondemented patients with cerebrovascular disease found a relation between microbleeds and executive dysfunction.¹³ Microbleeds are presumed to reflect cerebral amyloid angiopathy, a type of cerebrovascular pathology found with an incidence of 80% to 98% in AD.^{34,35} In the current study, we did not find a higher prevalence of microbleeds and patients who progressed to AD compared with nonconverters. Nonetheless, our results suggest that microbleeds are a risk factor for progression to a non-Alzheimer dementia.

Among the limitations of this study is the use of visual rating scales of MRI markers. Volumetric measures of MTA and WMHs could lead to different effect sizes, at the cost of being less generalizable to clinical practice. A complex issue is the role of MRI in the follow-up diagnosis, even though the diagnosis of dementia basically is a clinical diagnosis. At baseline none of the patients fulfilled the clinical criteria of dementia, and progression to dementia itself will not have been influenced by the MRI scan. In assessing the specific dementia types, MRI may have been used as a supportive element and therefore may have induced some circularity. This is especially the case for VaD, as current criteria require evidence of cerebrovascular disease on imaging.¹⁶ Any study assessing the risk of progression to at least VaD might consequently suffer from some degree of circularity. However, we think that the influence of this circularity is limited, as the clinical diagnosis of the specific dementia types was fundamentally based on the clinical picture and not on MRI. Unfortunately, we have no neuropathologic confirmation of our diagnoses, and it must be noted that patients with dementia frequently have shown multiple brain pathologies.³⁶ We demonstrated in this study that patients with vascular abnormalities on baseline MRI were more likely to develop non-Alzheimer dementia, mostly VaD. Still, it is conceivable that a large proportion of patients in fact suffered from mixed disease. Future research incorporating neuropathologic confirmation is needed to answer this question. Another limitation is the absence of clinical characterization of the MCI

cases into subgroups (amnesic/nonamnesic, single domain/multiple domain).³⁷ The clinical subtype may be related to the type of dementia (AD vs non-Alzheimer dementia) a MCI patient is most likely to progress to. Future research should be aimed to find out if the MRI determinations (of atrophy and cerebrovascular disease) add predictive value over this clinical MCI characterization.

Compared with the conversion rate of 12% per year reported by Petersen et al,¹ the conversion rate of almost 25% in our group of MCI patients seems rather high. However, our results are comparable to the conversion rate of other memory clinics,^{38,39} whereas the conversion rate reported by Petersen et al¹ was found in a general community setting.

A strong element is the exploration of the influence of a broad range of vascular abnormalities on MRI, including infarcts, WMHs, lacunes, and microbleeds. We adjusted analyses for age and sex and additionally for MMSE and MTA without essential change in the results. Furthermore, we included more MCI patients than most previous reports, including a considerable number of patients who progressed to non-Alzheimer dementia. However, the group of 16 patients was not large enough to allow examination of progression to specific dementia types other than AD. To conclude, in the clinical setting of a memory clinic, one should be aware of cerebrovascular disease, as it appears to be an important predictor of progression to non-Alzheimer dementia.

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Disclosures

None.

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