Vascular Subcortical Hyperintensities Predict Conversion to Vascular and Mixed Dementia in MCI Patients

Stéphanie Bombois, MD, PhD; Stéphanie Debette, MD; Amélie Bruandet, MD; Xavier Delbeuck, PhD; Christine Delmaire, MD, PhD; Didier Leys, MD, PhD; Florence Pasquier, MD, PhD

Background and Purpose—Patients with mild cognitive impairment (MCI) have an increased risk of dementia. The identification of predictors of conversion to dementia is therefore important. The aim of our study was to test the hypothesis that subcortical hyperintensities (SH) are associated with an increased rate of conversion to dementia in MCI patients.

Methods—This was an observational study on consecutive MCI patients attending a memory clinic. We assessed SH on a baseline MRI scan, using a semiquantitative rating scale. A multivariable Cox regression model was used to test the association of SH with conversion to dementia.

Results—We included 170 MCI patients. The median duration of follow-up was 3.8 years. During this period, 67 patients (39.4%, 95% CI: 32.1 to 46.8%) developed dementia: Alzheimer disease (AD) in 29 patients, dementia with Lewy bodies in 19, mixed dementia in 8, vascular dementia in 7, fronto-temporal dementia in 2, and primary progressive aphasia in 2. SH were not associated with the risk to develop dementia as a whole, including AD. However, the risk to develop vascular or mixed dementia increased significantly with increasing amounts of SH at baseline (HR = 1.14 [95% CI: 1.06 to 1.24]), especially periventricular hyperintensities (HR = 2.71 [95% CI: 1.60 to 4.58]), independently of medial temporal lobe atrophy, age, gender, vascular risk factors, education, and cognitive functions at baseline.

Conclusion—The risk of vascular or mixed dementia, but not of other types of dementia, was significantly increased in MCI patients with a large amount of subcortical hyperintensities at baseline. (Stroke. 2008;39:2046-2051.)

Key Words: mild cognitive impairment ■ subcortical vascular lesions ■ conversion ■ vascular dementia ■ Alzheimer disease

Mild cognitive impairment (MCI) is a transitional state between normal aging and early dementia.1 It is assumed to be pathology-based and possibly modifiable by intervention. Various MCI subtypes were defined according to the profile of impaired cognitive function, each subtype corresponding to the prodromal state of different types of dementia. Thus, amnestic single domain MCI often corresponds to an early stage of Alzheimer disease (AD), amnestic multiple domain MCI to early AD or vascular dementia (VD), nonamnestic single domain MCI to early dementia with Lewy bodies (DLB) or frontotemporal lobe degeneration, and nonamnestic multiple domain MCI to early DLB or VD.1 However, not all MCI patients convert to dementia, and some may recover a normal cognitive status or remain stable for years.2 In amnestic MCI patients, poorer cognitive performances7 and especially abnormal performances on cued memory task,8 hippocampal and entorhinal atrophy,9 or APOE ε4 allele6,7 were found to predict conversion to dementia. There is much less data on predictors of conversion to dementia in nonamnestic MCI, and on conversion of MCI patients to non-AD dementia.

Although population-based studies have suggested that silent brain infarcts and cerebral white matter lesions increase the risk of dementia in elderly people,10–12 the question of whether subcortical hyperintensities predict conversion to dementia in MCI patients is still unresolved. Two studies have investigated the association of subcortical lesions with conversion to dementia in MCI patients,13,14 providing conflicting results. In a previous paper, we have shown that the annual rate of global cognitive decline in MCI patients was higher with increasing amounts of subcortical, and especially periventricular hyperintensities on cerebral MRI at baseline, irrespective of the MCI subtype.15 The aim of the present study was to test the hypothesis that subcortical hyperintensities are associated with an increased rate of conversion to dementia in MCI patients.

Methods—We conducted this observational study in consecutive patients diagnosed with MCI during their first evaluation at the Lille Memory Clinic.
Clinic, between 1997 and 2004. We defined MCI by the presence of at least 1 cognitive test scoring below the commonly accepted cut-off of 1.5 standard deviations under the normal value, with global test scores in the normal range and no significant consequence on daily living activities. The following subtypes of MCI were identified: amnestic single domain, amnestic multiple domain, nonamnestic single domain, and nonamnestic multiple domain. We prospectively collected demographic characteristics, vascular risk factors, and history of vascular disease using a standardized questionnaire. Arterial hypertension was defined as a blood pressure value >140/90 mm Hg (or >130/80 mm Hg in diabetics) at rest on 2 separate measurements, or a current antihypertensive therapy; diabetes mellitus as a fasting blood glucose level >7.00 mmol/L on 2 separate occasions, or a current antidiabetic therapy; hypercholesterolemia as a total cholesterol level >5.93 mmol/L, or a current cholesterol lowering therapy. We excluded patients with history of stroke or transient ischemic attack or silent territorial cortical infarcts, but not those with silent subcortical infarcts.

Global cognition was assessed with the Mini Mental State Examination (MMSE) and the Mattis Dementia Rating Scale (DRS). Memory, attention, executive functions, visuospatial abilities, language, and praxis were evaluated in all patients using a neuropsychological battery detailed in previous publications. All patients had an MRI scan at baseline on a 1.5 Tesla machine (T2-weighted, spin-echo, and fluid attenuation inversion recovery [FLAIR] sequences; TE: 20 and 60 ms, TR: 2500 ms, section thickness: 5.0 mm). Subcortical hyperintensities (SH) were assessed on FLAIR imaging by an investigator blinded to the cognitive status of the patients (S.B.), using a previously validated semiquantitative rating scale. T2-weighted imaging was used to validate or not hypointensities on Flair sequences as vascular lesions. In addition to the total amount of subcortical hyperintensities (SH, range: 0 to 84), 4 subtypes of subcortical hyperintensities were assessed: periventricular hyperintensities (PVH, range: 0 to 6), white matter hyperintensities (WMH, range: 0 to 24), hyperintensities in the basal ganglia (BG, range: 0 to 30), and infratentorial hyperintensities (ITF, range: 0 to 24). The intrarater weighted kappa for SH, determined on 31 MRI-scans, was good ($\kappa=0.62$ [95% CI: 0.48 to 0.77]), as previously reported. This scale was shown to correlate well with volumetric measurements. We also assessed medial temporal lobe atrophy, using another previously validated semiquantitative rating scale. Medial temporal lobe atrophy was previously shown to be associated with conversion to dementia in MCI patients and is also associated with white matter lesions. It is therefore a potential confounder that should be adjusted for when evaluating the relationship between subcortical hyperintensities and conversion to dementia.

We followed-up all patients at least once a year. At each visit, we repeated the same standardized neurological and neuropsychological evaluation and evaluated the autonomy in activities of daily living. Additional structural brain imaging and functional brain imaging (SPECT) were performed when clinically indicated. We collected information on incident strokes and transient ischemic attacks. We diagnosed dementia using: (1) the National Institute of Neurological and Communication Disorders-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible AD, (2) the McKeith criteria for probable or possible DLB, (3) the Lund and Manchester criteria for frontotemporal dementia, (4) the Mesulam criteria for primary progressive aphasia, (5) the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria for VD. Because we excluded patients with a history of stroke, the disease onset was subtle and the course of the cognitive decline variable. Therefore, according to the NINDS-AIREN criteria, only possible VD could be diagnosed. There are no international diagnostic criteria for the diagnosis of mixed dementia (MD). However, in the NINDS-AIREN criteria, the term AD with cerebrovascular disease (CVD) is reserved to patterns fulfilling the clinical criteria of possible AD who have also clinical and imaging signs of relevant CVD. In the present study, we diagnosed mixed dementia in patients with an AD-type cognitive profile in addition to a prominent executive dysfunction on neuropsychological assessment, and with either hyperintensities in a strategic area known to be associated with cognition (such as the thalamus) or multiple subcortical hyperintensities in the white matter on cerebral MRI. The final diagnosis was reviewed by a multidisciplinary board including neurologists, psychiatrists, neuropsychologists, and speech therapists. Statistical analyses were performed with the SAS 8.02 software package (SAS Institute Inc). All tests were 2-tailed, a probability value of <0.05 being considered as statistically significant. The bivariate comparisons between groups were performed with the Chi-square test for qualitative variables and the Kruskal-Wallis test for continuous variables. We studied subcortical hyperintensities firstly as a continuous and secondly as a binary variable (the median of the distribution being used as a cut-off). We used a univariate and multivariable Cox regression model to test the association of subcortical hyperintensities with conversion to dementia. The multivariable model was adjusted for age, gender, educational level, vascular risk factors, medial temporal lobe atrophy, memory, and executive dysfunction at baseline, as well as baseline DRS score (as a marker of baseline global cognitive functions). The duration of follow-up corresponds to the time between the first and the last visit in the memory clinic for nonconverters and to the time between the first visit to the memory clinic and the estimated date of conversion to dementia for converters (data are right-censored at the date of conversion to dementia). For the statistical analyses vascular and mixed dementia were studied together because of small numbers.

### Results

We included 170 patients (98 women, median age: 68.1 years [range: 45.5 to 87.0], median MMSE score at baseline: 28 [26 to 30]). The MCI subtypes were amnestic single domain in 36 (21.2%) patients, amnestic multiple domain in 89 (52.3%) patients, nonamnestic single domain in 37 (21.8%) patients, and nonamnestic multiple domain in 8 (4.7%) patients. The median duration of follow-up was 3.8 [0.7 to 9.4] years. At the end of this period, 7 (4.1%) patients were left without any complaint and cognitive deficit, 3 (1.8%) had a memory complaint without objective cognitive deficit, 93 (54.7%) had MCI and 67 (39.4%, 95%CI: 32.1 to 46.8%) had become demented, with probable AD in 29 (43.3%), DLB in 19 (28.4%) (15 probable DLB, 4 possible DLB), mixed dementia in 8 (11.9%), possible VD in 7 (10.4%), and frontotemporal dementia and primary progressive aphasia in 2 patients, respectively (3.0%). Among the 170 patients, 33 nonconverters and 22 converters had a follow-up imaging. This second MRI scan was not used in our analysis of the association between subcortical hyperintensities and conversion to dementia. Our study is an observational study, and a second imaging is not systematically warranted in the daily care of demented patients. The main characteristics of converters and nonconverters are presented in Table 1. During follow-up, 3 patients had transient ischemic attacks (1 remained stable and 2 became demented).

The mean value and the range of SH in each location in nonconverters and in converters within the main subtypes of dementia is depicted in Figure 1, showing larger mean values of SH at baseline in patients who subsequently developed VD and MD compared to patients who did not. The overlapping ranges of SH values in patients with different types of dementia reflect the fact that the diagnosis of VD or MD was not based on SH values alone, but on a whole set of arguments, including neuropsychological profile and cognitive history.
In an univariate Cox regression model, there was a weak borderline significant association of subcortical hyperintensities with an increased risk to develop any type of dementia (HR = 1.03, 95% CI: 1.00 to 1.07). In a multivariable Cox regression model, executive dysfunction, lower DRS score, and temporal lobe atrophy at baseline, but not subcortical hyperintensities, significantly predicted conversion to dementia (Table 2). When studying the different types of dementia, increasing amounts of SH at baseline were significantly associated with an increased risk to develop vascular or mixed dementia (HR = 1.14 [95% CI: 1.07 to 1.22], Table 3), but not other types of dementia (data not shown). After adjustment for age, gender, educational level, and temporal lobe atrophy the association between SH and conversion to dementia remained significant.

### Table 1. Main Characteristics of Converters and Nonconverters

<table>
<thead>
<tr>
<th></th>
<th>Nonconverters</th>
<th>Converters</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>103</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>64.9 (45.5 to 81.0)</td>
<td>71.4 (46.2 to 87.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>55 (53.4%)</td>
<td>43 (64.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>50 (48.5%)</td>
<td>26 (38.8%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (17.5%)</td>
<td>13 (19.4%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (13.6%)</td>
<td>8 (11.9%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Educational level &lt;8 years</td>
<td>43 (41.8%)</td>
<td>25 (37.3%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Family history of dementia</td>
<td>28 (27.2%)</td>
<td>20 (29.9%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Follow-up, years*</td>
<td>4.5 (1.0 to 9.4)</td>
<td>3.4 (0.7 to 7.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Medial temporal lobe atrophy*</td>
<td>1 (0 to 3)</td>
<td>2 (0 to 3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Memory dysfunction</td>
<td>68 (66.0%)</td>
<td>57 (85.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>38 (36.9%)</td>
<td>34 (50.8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Amnestic–single domain MCI</td>
<td>25 (24.2%)</td>
<td>11 (16.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amnestic–multiple domain MCI</td>
<td>43 (41.8%)</td>
<td>46 (68.6%)</td>
<td></td>
</tr>
<tr>
<td>Non amnestic–single domain MCI</td>
<td>32 (31.1%)</td>
<td>5 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Non amnestic–multiple domain MCI</td>
<td>3 (2.9%)</td>
<td>5 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Baseline MMSE score*</td>
<td>28 (26 to 30)</td>
<td>28 (26 to 30)</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline DRS score*</td>
<td>138 (120 to 144)</td>
<td>135 (122 to 143)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ-MMSE, mean±SD**</td>
<td>0.1±0.5</td>
<td>−0.9±1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ-DRS, mean±SD**</td>
<td>0.2±2.4</td>
<td>−2.5±3.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are No. of patients (percentage), unless specified; *median (range); **mean±SD. The maximum score is 3 for medial temporal lobe atrophy, 30 for the baseline MMSE score, and 144 for the baseline DRS score. MMSE indicates Mini-Mental State Examination; DRS Dementia Rating Scale; Δ-score, difference between the mean score at the last visit and the mean score at baseline, divided by the duration of follow-up in years.

**Figure 1.** Mean value of subcortical hyperintensities in nonconverters and in patients converting to Alzheimer type dementia, to mixed or vascular dementia and to other types of dementia. SH indicates subcortical hyperintensities (total amount); PVH, periventricular hyperintensities; WMH, white matter hyperintensities; BG, basal ganglia hyperintensities; ITF, infratentorial foci of hyperintensity; VD, vascular dementia; MD, mixed dementia; AD, Alzheimer disease; DBL, dementia with Lewy bodies; OTH, other types of dementia. Vertical bars represent the range, the horizontal bars the median.
vascular or mixed dementia was unchanged (HR = 1.11 [95% CI: 1.04 to 1.20]). Similar results were found after adjusting additionally for vascular risk factors (HR = 1.13 [95% CI: 1.05 to 1.22]), and cognitive functions at baseline (HR = 1.14 [95% CI: 1.06 to 1.24]; Table 3). The results were also similar when excluding from the analysis subjects who developed another type of dementia (HR = 1.11 [95% CI: 1.03 to 1.20]). Thus, SH were more diffuse at baseline in MCI patients who subsequently converted to VD or MD compared to MCI patients who did not convert to dementia. The association of SH with conversion to vascular or mixed dementia did not differ significantly according to the presence or absence of memory or executive dysfunction at baseline (P for interaction = 0.09 and 0.78, respectively). When testing the association of the different subtypes of SH according to their location, using the same multivariable model, we found that both PVH (HR = 2.71 [95% CI: 1.60 to 4.58]) and WMH (HR = 1.16 [95% CI: 1.06 to 1.28]), but not BG or ITF, significantly predicted conversion to VD or MD. When studying conversion to VD and MD separately, a similar trend was found in both cases (HR = 1.20 [95% CI: 0.97 to 1.48] for the association of SH with VD, and HR = 1.24 [95% CI: 0.99 to 1.53] for the association of SH with MD).

When subcortical hyperintensities were studied as a binary variable, 2 of 84 patients with SH ≤6 (median of the distribution), and 13 of 86 patients with SH >6 developed vascular or mixed dementia. Compared to subjects with SH ≤6, the risk to develop vascular or mixed dementia was increased (HR = 10.00 [95% CI: 1.55 to 64.39]) in subjects with SH >6, independently of medial temporal lobe atrophy, age, gender, vascular risk factors, education, memory, and executive dysfunction, and DRS score at baseline (Figure 2).

All these results remained unchanged after exclusion of the 15 patients who did not convert to dementia and had a follow-up of less than 2 years.

**Discussion**

The present study showed that large amounts of periventricular and deep white matter hyperintensities at baseline were significantly associated with subsequent conversion to vascular and mixed dementia in consecutive MCI patients attending a memory clinic. This was independent of age, gender, vascular risk factors, educational level, medial temporal lobe atrophy, and cognitive functions at baseline. Subcortical hyperintensities were not associated with conversion to other types of dementia, including AD.

Our study has some limitations. Although patients were followed-up for more than 3 years on average, it is probable that some patients classified as nonconverters would have
developed dementia after a longer follow-up period. This, as well as insufficient statistical power, may have hampered our ability to detect an association of SH with dementia other than of vascular or mixed origin, especially AD. Although we have no pathological proof of the dementia type for most patients in this series, the accuracy of the clinical diagnosis of dementia in our center has been assessed in 100 consecutive patients who came to autopsy between 1993 and 2007, and was 80.0% for DBL (n = 15), 93.3% for MD (n = 15), 93.8% for AD (n = 32), and 100% for VD (n = 3) (Deramecourt V, personal communication, 2007). The fact that our memory clinic is a regional referral center, non-AD dementia probably accounts for the large proportion of DLB in the present study. As our study is retrospective and APOE ε4 is not warranted for the diagnosis of dementia, this factor was not included in our analyses. However, even though APOE ε4 has been suggested to predict conversion of amnestic MCI patients to Alzheimer disease, when cognitive performances are taken into account, predictive models with or without the APOE ε4 status were shown to have a similar accuracy. Moreover, there are no data on the predictive value of APOE ε4 on conversion to dementia in nonamnestic MCI. The lack of information on APOE ε4 status in the present analyses is therefore unlikely to be a strong bias.

Compared to the few previous studies that assessed the impact of subcortical lesions on conversion to dementia in MCI patients, the study described herein was performed on a larger population and is the first to test the association of subcortical lesions with conversion to different types of dementia. One previous study found an association between white matter changes on CT-scan and conversion to AD in 27 MCI patients. Another study failed to demonstrate any association between vascular lesions on cerebral MRI and conversion to dementia in 52 MCI patients and found that the impairment in memory and executive performance were the best predictors of conversion. Compared to the first study where white matter changes were probably quite extensive to be visible on CT-scan, large volumes of white matter lesions were uncommon in the second study, reducing the power to detect an effect of these lesions. Furthermore, none of these studies assessed the relationship between subcortical lesions and conversion to different types of dementia. In line with DeCarli et al., we found no association between subcortical hyperintensities and conversion to any type of dementia, the best predictors being medial temporal lobe atrophy, baseline executive dysfunction, and DRS score. We did, however, demonstrate that a large amount of subcortical hyperintensities in the periventricular and deep white matter independently predicted subsequent conversion to vascular or mixed dementia. This association was not assessed by DeCarli et al. The outcome measure they used was the Clinical Dementia Rating Scale (CDR), which, as mentioned by the authors, emphasizes memory-related cognitive impairment common to AD, suggesting that most cases of dementia in this cohort actually were AD. The criteria used for the diagnosis of dementia in the present study were wider and included specific criteria for other types of dementia than AD, enabling us to detect an association between subcortical hyperintensities and vascular and mixed dementia. This could also explain why we found an association of executive but not memory dysfunction with conversion to dementia.

Our results suggest that, among MCI patients attending a memory clinic, subcortical vascular lesions independently predict the subsequent occurrence of vascular and mixed dementia, but do not significantly influence conversion to other types of dementia, such as AD or DBL. This association needs to be confirmed in other independent MCI populations. If it is replicated, only a therapeutic trial aiming to reduce the white matter lesion load could prove that the relationship is causal. In case of coexisting neuropathological AD lesions, it could be hypothesized that subcortical vascular lesions influence conversion to dementia only if their progression rate is faster than the progression rate of AD lesions. Lesion severity at baseline being the main predictor of SH progression, one would expect SH to influence conversion to dementia mainly in patients with large amounts of SH at baseline. In other cases, AD lesions probably overwhelm the effect of subcortical lesions and become the major determinant of dementia. In our cohort, patients with dementia fulfilling both criteria for AD and DBL were classified as MD. Accordingly, patients diagnosed as “pure” AD were less likely to have extensive and rapidly evolving SH (see Figure 1) that may accelerate the shift from MCI to dementia. Future studies with repeated MRI scans are warranted to explore this hypothesis. Future studies assessing the independent effect of lacunes and WMH on progression of MCI patients to dementia could also be of interest. Recent publications have indeed suggested that these 2 types of subcortical lesions may be independently related to cognitive function in elderly community subjects, and that lacunes, but not WMH, could be associated with cognitive performance in MCI patients with milder medial temporal lobe atrophy.

In conclusion, increasing amounts of periventricular and deep white matter hyperintensities at baseline predicted conversion to vascular and mixed dementia in MCI patients attending a memory clinic. Even though validation of our results in independent populations is required, they suggest that MCI patients with diffuse subcortical hyperintensities at the initial evaluation ought to be followed-up more closely, because they seem to be at higher risk of conversion to vascular or mixed dementia. Subcortical lesions should also be taken into account in therapeutic trials targeting MCI patients.

Acknowledgments

The authors thank Nathalie Jourdan for the monitoring of the database.

Disclosures

None.

References

Subcortical Lesions and Conversion to Dementia


Vascular Subcortical Hyperintensities Predict Conversion to Vascular and Mixed Dementia in MCI Patients
Stéphanie Bombois, Stéphanie Debette, Amélie Bruandet, Xavier Delbeuck, Christine Delmaire, Didier Leys and Florence Pasquier

Stroke. 2008;39:2046-2051; originally published online April 24, 2008;
doi: 10.1161/STROKEAHA.107.505206
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/39/7/2046

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/