White Matter Lesions Are Associated With Progression of Medial Temporal Lobe Atrophy in Alzheimer Disease

Frank-Erik de Leeuw, MD; Esther Korf, MD; Frederik Barkhof, MD; Philip Scheltens, MD

Background and Purpose—Medial temporal lobe atrophy (MTA) is a hallmark of Alzheimer disease (AD). Its progression is often seen during the course of AD, but its frequency and risk factors remain unclear.

Methods—We investigated MTA in 35 patients with AD from whom sequential magnetic resonance imaging scans were available. White matter lesions (WML; for the periventricular [PV] and subcortical [SC] regions separately) and MTA were rated semiquantitatively.

Results—In approximately two thirds of all patients, progression of MTA was found. The mean MTA progression was 0.8 (standard deviation: 0.5) and 0.3 (standard deviation: 0.4) for patients with or without PVWML at baseline (P = 0.01). Patients who showed progression of PVWML over the course of their disease had a significantly higher mean progression of MTA than those without PVWML progression (0.9 [SD: 0.4]) and 0.4 [SD: 0.5]; P = 0.01). Patients with PVWML at baseline had a 40-fold increased risk for progression of MTA compared with those without baseline PVWML (odds ratio = 40.0, 95% CI = 1.3 to 1.2 × 10^4, P = 0.03). Patients with progression of PVWML during the course of the disease had an increased risk for MTA progression (odds ratio = 3.7 per unit increase of progression of PVWML, 95% CI = 1.1 to 12.9, P = 0.04). There was higher risk for progression of MTA for those with progression of PVWML than those without (odds ratio = 10.9, 95% CI = 1.0 to 122.5, P = 0.05). This was not found for SCWML.

Conclusions—Our findings suggest that the presence and the progression of WML are associated with progression of MTA in AD. WML may be a predictor of the course of the disease and a potential treatment target in AD. (Stroke. 2006;37:2248-2252.)

Key Words: aging ■ Alzheimer disease ■ small-vessel disease ■ white matter

Medial temporal lobe atrophy (MTA) is one of the first changes seen in the brains of patients with Alzheimer disease (AD). Its presence has proven to be a sensitive marker for the diagnosis of AD and also for future development of AD in patients with mild cognitive impairment. Progression of AD is paralleled by progression of MTA. There is very little known on factors that influence MTA progression.

Observational studies show an increased burden of amyloid plaques and neurofibrillary tangles by severity of MTA during the course of AD, but prospective follow-up studies on the frequency and risk factors for MTA progression to assess causality are lacking. Identification of potential modifiable risk factors for MTA progression is of importance to help advise patients and their relatives on what to expect from the disease in the near future and in terms of potential future treatments.

Potential risk factors for MTA progression include white matter lesions (WML) in view of a recently described relation between WML and MTA in a cross-sectional study. Given that in the course of AD, WML also progress over time, progression of WML may also be a risk factor for progression of MTA. If a causal relation between WML and MTA progression is to be proven, MTA progression may be prevented by modifying the progression of WML by, for example, treatment of the vascular risk factors for WML such as hypertension.

We hypothesized that the presence of WML at baseline and their progression along the course of AD are associated with MTA progression. We therefore wanted to investigate the frequency distribution of MTA progression among patients with AD and the relation between baseline and progression of WML and the progression of MTA in a prospective cohort of patients with AD.

Methods

Study Population
We investigated patients with AD from a prospective study on AD at the secondary/tertiary referral Alzheimer Center of the VU University Medical Centre in Amsterdam who all underwent serial MRI scanning. As part of a routine diagnostic procedure, all patients underwent a standardized workup involving history-taking, physical

Received February 27, 2006; final revisions received April 6, 2006; accepted June 7, 2006.
From the Department of Neurology (F.E.d.L.), University Medical Center St. Radboud, Nijmegen, The Netherlands; the Alzheimer Center and the Department of Neurology (F.E.d.L., E.K., P.S.), VU Medical Center, Amsterdam, The Netherlands; and the Department of Radiology (F.B.), VU Medical Center, Amsterdam, The Netherlands.
Correspondence to Frank-Erik de Leeuw, MD, Department of Neurology (HP326), University Medical Center St. Radboud, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail h.deleeuw@neuro.umcn.nl
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Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000236555.87674.e1

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and neurological examination, blood tests (erythrocyte sedimentation rate, hemoglobin, white cell count, serum electrolytes, glucose, urea, creatinine, liver function tests, thyroid stimulation hormone and free thyroid hormone, vitamin B1 and B6 levels, lues reactions), Mini Mental State Examination (MMSE),7 neuropsychologic examination, structural imaging of the brain, and a quantitative electroencephalogram. Final diagnosis was based on a consensus meeting in which all the available clinical data and the results of the ancillary investigations were considered. A diagnosis of probable AD was based on the NINCDS-ADRDA criteria.8 All patients provided written informed consent for their clinical data being used for research. We identified 35 of 252 consecutive patients with "probable" AD who had serial MRI scans available (mean follow up: 2.2 years; range: 1.0 to 5.1 years).

MRI Study Protocol
All subjects underwent a cranial MRI, including coronal T1-weighted and transverse proton density or fluid-attenuated inversion recovery images on a 1.0-T scanner (Impact; Siemens AG) using a standardized protocol, including contiguous 3-mm-thick slices for the T1 coronal images and 5-mm-thick slices with an interslice gap of 20.0% for the proton density and fluid-attenuated inversion recovery images. All sequences yielded an in-plane resolution of 1×1 mm². The second scan was made on the same machine with an identical protocol. The images were printed as hard copy with a reduction factor of 2.7.

WML Rating Scale
WML were rated using the Rotterdam Scan Study Rating Scale.9 The rater was blind to any clinical information of the patient. WML were considered present if these were hyperintense on proton density or fluid-attenuated inversion recovery images without prominent hypointensity on T1-weighted images. WML were assessed according to location in subcortical (SC) and periventricular (PV) regions using a previously described protocol.9 In short, the number and size of SCWML was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3 to 10 mm), or large lesions (>10 mm). A total volume of SCWML was calculated by considering them spherical as described previously.9 PVWML were rated semiquantitatively per region: adjacent to frontal horns (frontal capping), adjacent to lateral wall of lateral ventricles (bands), and adjacent to occipital horns (occipital capping) on a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining), to 3 (large confluent WML). The overall degree of PVWML was calculated by adding up the scores for the three separate regions (range: 0 to 9). Intrarater kappas for PVWML severity grades were between 0.6 and 0.8. The intrarater intraclass correlation coefficient for SCWML rating was 0.95.

TABLE 1. Characteristics of the Study Population at Baseline With or Without Serial MRI*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Follow Up</th>
<th>Without Follow Up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>35</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>66.2 (8.6)</td>
<td>72.3 (9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Women (%)</td>
<td>42.9</td>
<td>60.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean duration of follow up (years; range)</td>
<td>2.2 (1.0 to 5.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median MTA baseline (range)</td>
<td>1.5 (0 to 3.5)</td>
<td>2.0 (0 to 4)</td>
<td>0.048</td>
</tr>
<tr>
<td>Median MTA follow up (range)</td>
<td>2.0 (0 to 3.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median delta MTA (range)</td>
<td>0.5 (−0.5 to 1.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median PVWML baseline (range)</td>
<td>1.0 (0 to 6)</td>
<td>1.0 (0 to 9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Median PVWML follow up (range)</td>
<td>2.0 (0 to 6)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median delta PVWML (range)</td>
<td>0.0 (0 to 3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median volume (mL) SCWML baseline (range)</td>
<td>0.04 (0 to 3.2)</td>
<td>0.03 (0 to 3.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Median volume (mL) SCWML follow up (range)</td>
<td>0.06 (0 to 3.9)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median volume (mL) delta SCWML (range)</td>
<td>0.01 (−0.3 to 0.9)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84.7</td>
<td>79.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>151.9 (23.8)</td>
<td>152.1 (23.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>84.1 (10.6)</td>
<td>85.7 (10.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>MMSE</td>
<td>21.1 (5.2)</td>
<td>19.9 (5.4)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Values are age- and gender-adjusted means (SD) or percentages. NA indicates not applicable.
TABLE 2. Mean Progression of MTA by Baseline and Progression of WML*

<table>
<thead>
<tr>
<th>Baseline PVWML</th>
<th>Progression PVWML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Mean MTA progression</td>
<td>0.3 (0.4)</td>
</tr>
<tr>
<td>n=17</td>
<td>n=18</td>
</tr>
<tr>
<td>Mean MTA progression</td>
<td>0.6 (0.5)</td>
</tr>
<tr>
<td>n=8</td>
<td>n=27</td>
</tr>
</tbody>
</table>

*Means are adjusted for age, gender, duration of follow up, and blood pressure. †P=0.01.

Medial Temporal Lobe Atrophy
MTA was rated on a 5-point scale (0 to 4) on a coronal T1-weighted image based on the width of the choroid fissure and the temporal horn and the height of the hippocampal formation.† The mean of the left and right MTA score was used in the analysis.

All MRI scans were rated by an experienced rater with good intrarater reliability (κ between 0.6 and 0.8).

Other Covariates
Blood pressure was measured manually in a standardized manner by means of a sphygmomanometer with the patient in a sitting position after 5 minutes of rest based on a single measurement. The first and the fourth Korotkoff sounds were used for the systolic and diastolic blood pressure, respectively. Hypertension was defined as a baseline systolic blood pressure ≥140 mm Hg and/or a baseline diastolic blood pressure ≥90 mm Hg and/or the baseline use of blood pressure-lowering medication. Global cognitive function was assessed by the MMSE.‡

Statistical Analysis
Progression of both WML and MTA was defined as an increase of 1 point or more on the rating scales between baseline and follow up. The Figure shows a typical example of MTA progression. We calculated the mean progression of MTA stratified on absence or presence of baseline and of progression of WML by means of age-and gender-adjusted analysis of variance. Odds ratios (ORs) were calculated to quantify the association between baseline and progression of WML (independent variable) and progression of MTA (dependent) by means of age- and gender-adjusted logistic regression analysis. Additional adjustments were made for the MMSE (as an indicator of dementia severity), systolic and diastolic blood pressure, and the duration of follow up. The relation between progression of WML and progression of MTA may be confounded by the severity of baseline WML because progression of WML has shown to be significantly related to baseline presence of WML and in patients with AD. We therefore performed additional adjustments for baseline WML in all analyses in which progression of WML was the independent variable.

TABLE 3. The Relative Risk for MTA Progression in Patients With AD by Baseline and Progression of WML (OR and 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>PVWML</th>
<th>SCWML</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline*</td>
<td>Progression†</td>
</tr>
<tr>
<td>Risk for progression of MTA</td>
<td>40.0 (1.3 to 1.2×10^3)‡</td>
<td>3.7 (1.1 to 12.9)§</td>
</tr>
</tbody>
</table>

*The reference group consists of patients without WML at baseline; †Per unit of WML progression; ‡P=0.03; §P=0.04.

Results
Patients with a follow-up scan were younger than those without (66.2 years, standard deviation [SD]: 8.6 versus 72.3 years, SD: 9.5, P<0.05). Roughly half of all patients were female both in the group with as well as without a follow-up scan. Mean MMSE at baseline was 21.1 (SD: 5.2). Other baseline characteristics are presented in Table 1. Except for age and MTA, there were no differences in baseline characteristics between those with or without follow-up MRI.

There were 25 patients (~70%) who showed MTA progression. Patients <70 years of age had a higher mean progression of MTA than those ≥70 years of age (0.7, SD: 0.5; and 0.3, SD: 0.5); however, this was not significant. There was no difference between men and women with respect to progression of MTA.

Progression of MTA was related to the presence of PVWML at baseline and to progression of PVWML. The mean MTA progression was 0.8 (SD: 0.5) and 0.3 (SD: 0.4) for patients with or without PVWML at baseline (P=0.01). Patients who showed progression of PVWML over the course of their disease had a significantly higher progression of MTA than those without PVWML progression (0.9, SD: 0.4; and 0.4, SD: 0.5; P=0.01). This was not found for SCWML (Table 2).

Patients with PVWML at baseline had a 40-fold increased risk for progression of MTA compared with those without baseline PVWML (OR=40.0; 95% CI=1.3 to 1.2×10^3, P=0.03). Patients with progression of PVWML during the course of the disease had an increased risk for MTA progression (OR=3.7 per degree increase of progression of PVWML, 95% CI=1.1 to 12.9, P=0.04). There was higher risk for progression of MTA for those with progression of PVWML than those without OR=10.9, 95% CI=1.0 to 122.5, P=0.05. This was not found for SCWML (Table 3).

Adjustment for confounding factors, including the degree of baseline WML, did not alter the magnitude of the association.

Discussion
We found that patients with WML at baseline and those with an increase of WML, especially the PVWML, over a mean 2-year period of follow up had a significantly higher risk for progression of MTA.

Strengths of our study are the prospective nature of the study and the fact that baseline and follow-up scans were rated independently from each other with high intrarater agreement.

Some methodological issues need attention. Selection bias may have influenced our findings in several ways. As a result of the nature of a follow-up study, only those participants who were still alive at follow up undergo serial MRI scanning. Therefore, it could be that selective survival of people with a...
relatively mild degree of WML at baseline and those with a relatively mild progression of WML has occurred because severity of WML is related to mortality.12 Another form of selection bias may be the underrepresentation of those patients who are in a more advanced stage of the disease and presumably have the highest degree of WML, because those patients are not very likely to show up at regular outpatient clinic controls and at repeated MRI examination, for example, as a result of mobility-related problems.13 However, we do not think that these forms of bias significantly influenced our findings because in a previous study, we found a linear relation between the degree of WML and MTA; consequently, those with the most severe WML would most likely to have the most severe MTA.

WML and MTA were rated with the Rotterdam Scan Study Scale9 and with a semiquantitative MTA rating scale, respectively,10 which both were not developed for the detection of change in a longitudinal design. The use of the Rotterdam Scan Study Scale for this purpose proved to be poor in a recent validation study,14 especially for the detection of change of PVWML, but performed better for the detection of change of SCWML. A reason for this could be the so-called ceiling effect that presumably does not apply to the SCWML. PVWML that were already rated in the highest category at baseline (and which are most likely to progress) cannot contribute to progression on these scales because they are already in the highest category, whereas SCWML were counted taking into account number and size of lesions without predefined maximum, thus avoiding a ceiling effect. However, the presumed influence of this ceiling effect is limited in our study because patients in our study had a median baseline PVWML of 1.0 (which is way below the maximum of 9.0) compared with 6.0 in the study of Prins et al.14

This type of validation study has never been done for the detection of MTA change over time with the semiquantitative MTA rating scale we used, but similar reasoning may apply, because mean MTA scores in our study were quite low and far below the maximum of the score.

Our finding of a relation between progression of WML and progression of MTA could be confounded by baseline WML because this has proven to be related to progression of WML.6,11 A reason for this could be the so-called ceiling effect that presumably does not apply to the SCWML. PVWML that were already rated in the highest category at baseline (and which are most likely to progress) cannot contribute to progression on these scales because they are already in the highest category, whereas SCWML were counted taking into account number and size of lesions without predefined maximum, thus avoiding a ceiling effect. However, the presumed influence of this ceiling effect is limited in our study because patients in our study had a median baseline PVWML of 1.0 (which is way below the maximum of 9.0) compared with 6.0 in the study of Prins et al.14

This type of validation study has never been done for the detection of MTA change over time with the semiquantitative MTA rating scale we used, but similar reasoning may apply, because mean MTA scores in our study were quite low and far below the maximum of the score.

Our finding of a relation between progression of WML and progression of MTA could be confounded by baseline WML because this has proven to be related to progression of WML.6,11 However, adjustment for baseline WML did not alter the magnitude of the association rendering this explanation unlikely. Our study does not provide an explanation on how WML may ultimately lead to MTA in AD. An explanation could be that the medial temporal lobe is disconnected from connected cortical areas by the vascular WML in the white matter tracts subserving the cortical association areas15,16 leading to shrinkage of the medial temporal lobe resulting from Wallerian degeneration. Despite the fact that ours is a prospective study, both WML and MTA were already present at baseline examination; therefore, causal inference on the underlying mechanism cannot be made from our study. It is not known why periventricular and subcortical WML would have a differential influence on MTA. An explanation could be that the periventricular WML affect areas of long fiber tracts that connect several distant cortical areas with each other (including the MTA),15,16 whereas subcortical WML mainly disrupt short loops of corticocortical connections not related to distant structures such as the MTA.17 Still, a remaining explanation for our finding includes the possibility of an identical underlying mechanism for both WML and MTA such as changes in the amyloid metabolism or vascular brain disease. The predominant pathology in MTA even early in the course of AD is the presence of amyloid plaques, whereas recent studies also indicated a relation between the level of cerebral amyloid deposition could both lead to progression of both WML and MTA, thereby explaining our finding. Another underlying mechanism may be that cerebral ischemia not only results in WML, but also in MTA. Indeed, pathologic studies found microinfarcts in the medial temporal lobe in patients with AD.20

Our findings suggest a relation between both baseline and progression of WML and progression of MTA. When our findings are substantiated, this may indicate that the presence of PVWML on an MRI scan can be used as a tool that is able to predict MTA progression (and as such, presumably progression of the disease) in still relatively mildly demented patients years before end stages of the disease. As such, they may function as a surrogate end point in clinical trials that aim at modifying the course of AD.21 If a causal relation between WML and MTA progression is to be proven, MTA progression may be prevented by modifying the progression of WML by, for example, treatment of the vascular risk factors for WML such as hypertension.22

Sources of Funding
The Alzheimer Center is supported by the VUMF funds; the stay of F.-E.d.L. was funded by the Stichting Alzheimer & Neuropsychiatry Foundation.

Disclosures
None.

References


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*Stroke*. 2006;37:2248-2252; originally published online August 10, 2006;
doi: 10.1161/01.STR.0000236555.87674.e1

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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