Periventricular Cerebral White Matter Lesions Predict Rate of Cognitive Decline

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The prospect of declining cognitive functions is a major fear for many elderly persons. Cerebral white matter lesions, as commonly found with magnetic resonance imaging, have been associated with cognitive dysfunction in cross-sectional studies. Only a few longitudinal studies using small cohorts confirmed these findings. We examined the relation between severity of white matter lesions and cognitive decline over a nearly 10-year period in 563 elderly subjects sampled from the general nondemented Dutch population. Severity of white matter lesions was scored for periventricular and subcortical regions separately using an extensive semiquantitative scale. Cognitive function was measured by the Mini-Mental State Examination at regular time intervals during 1990 to 2000, and magnetic resonance imaging scans were made in 1995 to 1996. More severe white matter lesions were associated with more rapid cognitive decline over a mean follow-up period of 7.3 years (standard deviation, 1.5). After adjusting for age, gender, educational level, measures of depression, and brain atrophy and infarcts, subjects with severe periventricular white matter lesions experienced cognitive decline nearly three times as fast (0.28 Mini-Mental State Examination points/year [95% confidence interval, 0.20–0.36]) as the average (0.10 points/year [95% confidence interval, 0.09–0.11]). There was no independent relationship between severity of subcortical white matter lesions and rate of cognitive decline.

Cardiovascular disorders are thought to play a role in the development of cerebral white matter lesions (WMLs), cognitive impairment, and dementia.1–3 From cross-sectional studies, there is considerable evidence for the association between WMLs and cognitive impairment in demented and nondemented elderly subjects.4–8 Confirmation from longitudinal studies is, however, scarce, with only two longitudinal population-based studies being published to date.9,10 Interpretation of findings from these studies is, however, restricted because of the highly selected study populations, because only a low percentage of subjects completed the study.

The white matter of the brain can be distinguished into the area just under the cortex (subcortical) and the area adjoining the ventricles (periventricular). WMLs in these two regions may affect cognition in different ways.11 In most of the research performed to date, WMLs have been rated and combined in a single score,4,5,12 or only one of the two regions has been taken into account.13–16 In a previous cross-sectional study, we found, in particular, periventricular WMLs related to lower cognitive function, whereas subcortical WMLs were related with depressive symptoms.8,17

The objective of this study was to investigate whether severity of WMLs is associated with the rate of cognitive decline and whether this association is different for periventricular WMLs as compared with subcortical WMLs. We based our study on a random sample of 563 nondemented Dutch elderly subjects aged 55 to 85 years at baseline of whom we have multiple measurements of cognitive function during a follow-up period of up to nearly 10 years.

Subjects and Methods

Study Population

From 1995 to 1996, a random sample (n = 1,904) of elderly nondemented persons aged between 60 and 90 years was invited by strata of age (5 years) and gender for the Rotterdam Scan Study as detailed previously.8,18 Subjects were recruited from two large ongoing cohort studies: the Zoetermeer Study and the Rotterdam Study.19,20 Because longitudinal data on cognitive function were available only for participants of the latter cohort study, this study incor...
oporates only participants from the Rotterdam Study. In short, the Rotterdam Study is a prospective population-based study among 7,983 elderly subjects aged 55 years and older, designed to study determinants of selected chronic diseases in the elderly.20 The Rotterdam Study had its baseline assessment in 1990 to 1993 and has regular follow-up examinations of which the first was in 1993 to 1994. From this cohort, 965 subjects were chosen randomly by strata of age and gender and invited for participation in the Rotterdam Scan Study. After excluding subjects with contraindications for participation (dementia, contraindications for magnetic resonance imaging [MRI]; scanning, blindness), 832 were eligible. MRI images were obtained for 563 of these eligible subjects (68%) in 1995 to 1996. Further follow-up examinations could be performed in 475 and 393 of these participants in 1997 to 1999 and 1999 to 2000, respectively. The study was approved by the medical ethics committee of the Erasmus University and each participant gave written consent.

The 269 eligible subjects who refused to participate in the Rotterdam Scan Study gave as main reasons old age, too much trouble, not wanting to participate in brain research, and claustrophobia. At the time of MRI assessment, responders (n = 563) were younger (mean age difference, 4.9 years; p < 0.001), were more educated (2.4% more subjects with university level education, p = 0.05), and had higher baseline Mini-Mental State Examination (MMSE)21 scores (age- and gender-adjusted mean difference, 0.4 points; p < 0.001) compared with nonresponding eligible subjects (n = 269) of the Rotterdam Scan Study.

Magnetic Resonance Imaging Scanning
Cerebral MRI scanning was performed in 1995 to 1996 on a 1.5T scanner (Magnetom VISION; Siemens AG, Erlangen, Germany). The scanning protocol included a series of axial proton density (TR, 2,200 milliseconds; TE, 20 milliseconds), T2-weighted (TR, 2,200 milliseconds; TE, 80 milliseconds), and T1-weighted (TR, 700 milliseconds; TE, 14 milliseconds) images. Sections were 5mm thick with an interslice gap of 20%. Laser hardcopies were printed with a reduction factor of 2.7.

Periventricular and subcortical WMLs were considered present if visible as hyperintense on both proton density and T2-weighted images, without prominent hypointensity on T1-weighted images. Details on the scoring method have been described previously.3,18 Briefly, WMLs were considered periventricular when their largest diameter was adjacent to the ventricular lining; otherwise, they were considered subcortical. Periventricular WMLs were scored semiquantitatively on a scale of 0 to 3 for lesions located adjacent to the occipital and frontal horns, and the lateral ventricles, separately. These region-specific scores were added for the total periventricular WML severity (range, 0–9). For subcortical WMLs, a total volume score was approximated based on the number and size (small [<3mm], medium [3–10mm], or large [>10mm]) of all subcortical lesions. Other recorded brain features were cerebral atrophy and the presence and number of cerebral infarcts. Subcortical atrophy was measured by the ventricle to brain ratio (range, 0.21–0.45). Cortical atrophy was rated semiquantitatively (range, 0–15). Cerebral infarcts were defined as hyperintense on T2-weighted images, with corresponding hypointensity on T1 (approaching the intensity of cerebrospinal fluid) and without hypointensity on proton density–weighted images. Intrareader and interreader studies showed a good to excellent agreement. Weighted ks for periventricular WML severity grades were between 0.79 and 0.90, and for cortical atrophy 0.81. Intrareader and interreader–intraclass correlation coefficients for subcortical WML volume were 0.88 and 0.95, and for cortical atrophy 0.57 and 0.76. Of the 563 participants, only 5% had no WMLs at all, whereas 16% were free of periventricular WMLs and 8% had no signs of subcortical WMLs; 76% of all participants had at least some degree of both periventricular and subcortical WMLs.

Measurement of Cognitive Decline
In the regular surveys of the Rotterdam Study, the MMSE is administered to all participants as part of the screening for dementia.22 The MMSE was included in the neuropsychological tests of the Rotterdam Scan Study. MMSE scores were not available for 8 (1%) and 5 (1%) of the participants at the examinations in, respectively, 1990 to 1993 and 1993 to 1994. After MRI assessment, two participants were lost to follow-up (one moved to the north of the Netherlands and another moved to Poland), 46 died, and 122 were observed for major end points but refused one or both of the reexaminations. The MMSE could be administered in 88% of the surviving participants of the Rotterdam Scan Study in 1997 to 1999 and in 76% of the surviving participants in 1999 to 2000. From the maximum of five MMSE measurements, one was missing in 23%, and two in 13% of participants. Mean duration of follow-up on cognitive function was 7.3 years (SD = 1.5; range, 2.4–9.7).

Other Measurements
Characteristics, obtained at the time of MRI assessment, considered as possible confounding variables were age, gender, level of education (according to the international standards of UNESCO),23 presence of depressive symptoms (defined as a score ⩾16 on the Center of Epidemiologic Studies Depression Scale),24 the neuroimaging characteristics cortical and subcortical atrophy, and the presence of cerebral infarcts on MRI.

Statistical Analysis
To assess the relation between the severity of WMLs and rate of cognitive decline, we first had to estimate each subject’s rate of decline at the time of MRI measurement. We did this with a random-effects model for repeated measures (PROC MIXED with residual maximum likelihood method; SAS Systems for Windows release 6.12; SAS Institute, Cary, NC) in which all available MMSE measurements were used as the outcome variable, and time of measurement as the independent variable (time = 0 at baseline examination). Rate of cognitive decline over the whole follow-up period was expressed as decline on the MMSE per year and calculated for each subject by adding the estimated fixed effect and the individual random effect.

The relation between WML severity and rate of cognitive decline subsequently was assessed by means of multiple re-
gression analyses (analysis of covariance and linear regression for test for trends) with adjustments for age, gender, level of education, presence of depressive symptoms, severity of brain atrophy and presence of cerebral infarcts. We used the same methods to analyze the relation between WML severity and baseline and concurrent (at the time of MRI assessment) MMSE scores.

For those persons who participated at the last MMSE assessment, we examined whether the rate of cognitive decline before MRI was different from thereafter. For this, we took the MMSE score at the first assessment and the score at the time of MRI and calculated the mean decline per year. Similarly, for the mean cognitive decline after MRI, we took the MMSE score at the time of MRI and the score at the latest assessment that was available. These two individual rates of cognitive decline were compared using a paired t test. We analyzed whether the relation between these two individual rates of decline had a different relation with WML severity by multivariate linear regression, adjusting for age and gender.

Periventricular and subcortical WMLs were scored differently, with periventricular lesions scored semiquantitatively with a score ranging from 0 to 9 and subcortical WMLs scored as a total volume. Therefore, to compare the strength of the association of either WML location with cognitive decline, we divided the severity distribution of both WML locations in equal categories. This was done both in quintiles of the distributions and, for more detailed analyses, according to the distribution of the actual severity scores of periventricular WMLs. For the latter, we created 10 categories for each different periventricular WML severity score (0–9) and 10 size-corresponding categories of increasing subcortical WMLs.

In additional analyses, we studied whether the relation between subcortical WMLs and cognitive decline was conditional on the severity of periventricular WMLs and vice versa. For this, periventricular and subcortical WMLs were entered simultaneously in the statistical models. Furthermore, because low baseline MMSE scores have been associated with an increased rate of cognitive decline as well as with WML severity, we performed additional analyses in which we adjusted for baseline MMSE scores.

Finally, with multiple regression analyses (analysis of covariance, adjusted for age and gender), we evaluated whether participation in follow-up examinations was related to rate of cognitive decline or WML severity. With age- and gender-adjusted multiple linear regression, we assessed the relation between cognitive function at baseline and at the time of imaging and rate of cognitive decline.

Table 1. Characteristics of Participants at the Time of Cerebral MRI Assessment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Participants (n = 563)</th>
<th>1997–1999 (n = 475)</th>
<th>1999–2000 (n = 393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics in 1995–1996</td>
<td></td>
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<tr>
<td>Mean age, yr (IQR)</td>
<td>73.5 (66.2–80.5)</td>
<td>72.6 (65.7–79.0)</td>
<td>72.2 (65.6–77.8)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>281 (50)</td>
<td>242 (51)</td>
<td>203 (52)</td>
</tr>
<tr>
<td>Subjects with only primary education (%)</td>
<td>174 (31)</td>
<td>140 (30)</td>
<td>108 (28)</td>
</tr>
<tr>
<td>Mean score on the CES-D (IQR)</td>
<td>5.6 (1–9)</td>
<td>5.6 (1–9)</td>
<td>5.5 (1–9)</td>
</tr>
<tr>
<td>Subjects with depressive symptomsa (%)</td>
<td>32 (6)</td>
<td>21 (4)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Mean score on the MMSE (IQR)</td>
<td>27.7 (27–29)</td>
<td>27.8 (27–29)</td>
<td>27.9 (27–29)</td>
</tr>
<tr>
<td>Mean rate of cognitive declineb (IQR)</td>
<td>0.103 (0.005–0.159)</td>
<td>0.095 (0.003–0.151)</td>
<td>0.083 (0.002–0.137)</td>
</tr>
<tr>
<td>Neuroimaging characteristics in 1995–1996</td>
<td></td>
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<tr>
<td>Mean volume of subcortical WML (IQR)</td>
<td>1.83 (0.04–2.12)</td>
<td>1.61 (0.03–1.80)</td>
<td>1.58 (0.03–1.85)</td>
</tr>
<tr>
<td>Mean total periventricular WML score (IQR)</td>
<td>2.8 (1.0–4.0)</td>
<td>2.6 (0.875–4.0)</td>
<td>2.5 (0.5–4.0)</td>
</tr>
<tr>
<td>Subjects with cerebral infarcts on MRI (%)</td>
<td>155 (28)</td>
<td>114 (24)</td>
<td>100 (25)</td>
</tr>
<tr>
<td>Mean grade of cortical atrophy (IQR)</td>
<td>1.2 (0.8–1.6)</td>
<td>1.2 (0.8–1.6)</td>
<td>1.2 (0.8–1.5)</td>
</tr>
<tr>
<td>Mean ventricle-to-brain ratio (IQR)</td>
<td>0.31 (0.28–0.33)</td>
<td>0.31 (0.28–0.33)</td>
<td>0.30 (0.28–0.33)</td>
</tr>
</tbody>
</table>

aDepressive symptoms defined as present when CES-D score was ≥16.
bDecline in MMSE score per year.

MRI = magnetic resonance imaging; IQR = interquartile range; CES-D = Center for Epidemiological Studies on Depression Scale; MMSE = Mini-Mental State Examination; WML = white matter lesion.
of cognitive decline after MRI compared with the rate of decline before MRI did not differ significantly (difference, −0.04; \(p = 0.35\)).

Neither concurrent nor baseline MMSE scores were different across severity quintiles of subcortical WMLs (\(p_{\text{trend}} > 0.79\) for both). Concurrent but not baseline MMSE scores were lower when more severe periventricular WMLs were present (\(p_{\text{trend}}\) across quintiles, 0.02 and 0.86, respectively), with a score difference of 0.6 (95% confidence interval [CI], 0.1–1.2) between lowest and highest periventricular WML quintile. Both concurrent and baseline MMSE scores were related to the rate of cognitive decline. Per point decrease in either of these cross-sectional MMSE scores, rate of cognitive decline was 0.05 higher (\(p < 0.001\)).

There was a positive association between severity of periventricular WMLs (in quintiles) and rate of cognitive decline (Table 2) with a rate difference of 50% between lowest and highest periventricular WML quintile (\(p = 0.002\)). For the corresponding subcortical WML quintiles, this difference did not reach statistical significance (\(p = 0.46\)). The association between periventricular WMLs and rate of cognitive decline remained when this was studied conditional on the severity of subcortical WMLs and when adjusted for baseline values of MMSE (see Table 2). For those persons who participated at the last MMSE assessment, we found no differences in the relations between the severity of periventricular WMLs and cognitive decline before or after MRI.

Figure 2A illustrates the association between the original severity scores (0–9) of periventricular WMLs and the 10 size-matched severity categories of subcortical WMLs and the rate of cognitive decline. Subjects with the most severe periventricular WMLs had a nearly tripled rate of cognitive decline (rate = −0.28/year [95% CI, −0.36 to −0.20]), and subjects with the most severe subcortical WMLs had a doubled rate of cognitive decline (rate = −0.21/year [95% CI, −0.29 to −0.13]) compared with the average (−0.10/year [−0.09 to −0.11]). When this relation between periventricular WMLs and rate of cognitive decline was analyzed conditional on the severity of subcortical WMLs and vice versa, the relation between the severity of subcortical WMLs and rate of cognitive decline disappeared (subjects with the most severe subcortical WMLs, rate = −0.15/year [95% CI, −0.24 to −0.07]). Adjusting these analyses for baseline MMSE scores only slightly diminished the strength of the association between the rate of cognitive decline and periventricular WMLs (see Fig 2C; rate of cognitive decline for most severe periventricular WMLs, −0.25/year [95% CI, −0.33 to −0.17]); for most severe subcortical WMLs, −0.17/year [95% CI, −0.23 to −0.09]).

Discussion

We investigated the relation between the severity of cerebral WMLs and decline in cognitive function in a large population-based sample of nondemented elderly persons and found that the severity of periventricular, but not subcortical WMLs, was related with the rate of cognitive decline.

Nonparticipants, compared with participants in our study, were older, had lower MMSE scores, and were less educated. Because these factors have been associated with WMLs as well as with cognitive decline, subjects with the most severe WMLs and the highest rate of cognitive decline probably are underrepresented in our study. Although it is possible that the relation between severity of WMLs and cognitive decline is different in nonparticipants, we consider this unlikely. Therefore, selection bias may have weakened the relation between severity of WMLs and rate of cognitive decline in our study. MMSE scores could not be obtained for all participants at all examinations. Because of death of participants, refusal, or loss to follow-up, participation was not complete during the last two reexaminations. Subjects who had died or had refused these reexaminations had lower MMSE scores, higher rates of cognitive decline, and more severe WMLs at the time of MRI assessment. Therefore, the calculated average rate of cognitive decline probably would have been higher if data collection would have been complete. Because of this, we may have underestimated the strength of the association between WMLs and rate of cognitive decline.

Although the MMSE originally was developed as a screening instrument for dementia, it has proved to be a reliable measure of global cognitive function, at least at a population level.25,26 Despite being a rough measure of global cognitive function, the severity of WMLs was associated with the rate of decline of the MMSE score and with the MMSE score at the time of imaging. The mean overall rate of decline was 0.10 MMSE points per year.
Most previous studies found relationships between WML and cognitive function only in a cross-sectional design.\textsuperscript{4,5,8,16,31} To date, two other population-based longitudinal studies reported on the relation between WML and cognitive decline.\textsuperscript{9,10} In the study by Swan and colleagues, a relationship between total WML volume and decline of MMSE scores is reported, based on two MMSE measurements. However, these investigators had not distinguished periventricular or subcortical regions of WMLs.\textsuperscript{9} Periventricular, but not subcortical WMLs, have been related atherosclerosis,\textsuperscript{32} and cognitive impairment has been related to periventricular WMLs, but not to subcortical WMLs,\textsuperscript{8,31} illustrating the importance of differentiating between WMLs at different locations. The mechanisms underlying these differences are not clear, but possibly the vascular architecture of the periventricular area is more vulnerable to damage than other white matter areas.\textsuperscript{2} Anatomically, the periventricular region has a high density of long associating fibers connecting the cortex with subcortical nuclei and other distant brain territories, whereas the subcortical area has a high density of short- looped U-fibers connecting adjacent cortical regions.\textsuperscript{33,34} Possibly reserve mechanisms might explain why lesions affecting connectivity between neighboring brain regions have less influence on cognitive functions than lesions affecting connectivity between distant brain areas. Garde and colleagues separated periventricular and subcortical WMLs in their ratings and used these in the analyses with multiple extensive neuropsychological measurements.\textsuperscript{10} They reported a relation between WML severity at both locations and cognitive decline. However, the relation between subcortical WMLs and cognitive decline was not analyzed conditional on the severity of periventricular WMLs, possibly explaining the reported relation between subcortical WMLs and cognitive decline. Also in their study cognitive decline was analyzed in three periods of a decade, not using the more powerful

Table 2. The Relation between WML Severity and Rate of Cognitive Decline

<table>
<thead>
<tr>
<th>Quintiles of WML Severity</th>
<th>n</th>
<th>Average Decline on the MMSE Score per Year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1\textsuperscript{a}</td>
</tr>
<tr>
<td>Periventricular First</td>
<td>125</td>
<td>-0.09 (-0.11 to -0.06)</td>
</tr>
<tr>
<td>Second</td>
<td>154</td>
<td>-0.08 (-0.10 to -0.06)</td>
</tr>
<tr>
<td>Third</td>
<td>78</td>
<td>-0.11 (-0.14 to -0.09)</td>
</tr>
<tr>
<td>Fourth</td>
<td>84</td>
<td>-0.11 (-0.14 to -0.08)</td>
</tr>
<tr>
<td>Fifth</td>
<td>122</td>
<td>-0.14 (-0.16 to -0.11)</td>
</tr>
<tr>
<td>Subcortical First</td>
<td>111</td>
<td>-0.09 (-0.12 to -0.06)</td>
</tr>
<tr>
<td>Second</td>
<td>115</td>
<td>-0.10 (-0.12 to -0.07)</td>
</tr>
<tr>
<td>Third</td>
<td>112</td>
<td>-0.10 (-0.12 to -0.07)</td>
</tr>
<tr>
<td>Fourth</td>
<td>112</td>
<td>-0.10 (-0.13 to -0.08)</td>
</tr>
<tr>
<td>Fifth</td>
<td>113</td>
<td>-0.13 (-0.15 to -0.10)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted for age, gender, level of education, presence of depressive symptoms, cerebral atrophy, and presence of cerebral infarcts.

\textsuperscript{b}As in model 1, but periventricular WML conditional on the severity of subcortical WML, and vice versa.

\textsuperscript{c}As in model 2, but additionally adjusted for MMSE score at baseline.

WML = white matter lesion; MMSE = Mini-Mental State Examination.
repeated-measures PROC MIXED analyses. Finally, only 21% of the eligible sample were available for their analyses, representing the healthiest persons of their birth cohort. This might explain the weak associations they found between WMLs and cognitive decline.

We found an association between periventricular but not subcortical lesions and rate of cognitive decline. One might wonder whether this results from the different scoring methods that we used for both types of lesions. We do not believe that that is the case. First, we evaluated both types of lesions categorized similarly, in quintiles and according to the severity distribution of periventricular lesions. Second, in a previous analysis on the relation between WMLs and depression, we found relations with subcortical WMLs, but not with periventricular WMLs. If differences in scoring methods were responsible for the different relations we found for periventricular and subcortical WMLs with cognitive decline, we also would have expected to find the relation with depression primarily for periventricular WMLs. Finally, it is neurobiologically plausible that damage to neural pathways in the periventricular locations has more influence on cognitive processes than damage to subcortical pathways, as discussed above.

We conclude that periventricular WMLs are associated with the rate of cognitive decline. This relation remained unaltered after controlling for other brain abnormalities (atrophy and cerebral infarcts) and other characteristics that could influence cognitive performance such as educational level and the presence of depressive symptoms. Possibly, the accelerated rate of cognitive decline found in the presence of severe periventricular WMLs is a prelude to the development of dementia. In the forthcoming years, researchers will be able to investigate whether periventricular WMLs are associated with an increased risk of dementia, as has been suggested from cross-sectional studies. Until that time, WML severity as a diagnostic marker has to be interpreted with caution. Because we made only a sin-

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**Fig 2.** The relation between severity of white matter lesions (WMLs) and cognitive decline. Severity of WML divided in 10 categories based on the distribution of periventricular WML scores. Cognitive decline expressed as rate of decline in Mini-Mental State Examination (MMSE) score per year (+standard error). (A) Adjusted for age, gender, level of education, presence of depression, cerebral atrophy, and cerebral infarcts (B) as in A, but periventricular WMLs conditional on severity of subcortical WMLs and vice versa; (C) as in B, but additionally adjusted for baseline MMSE score. (squares) Periventricular WML; (circles) subcortical WML. Number of subjects in consecutive periventricular WML severity categories was 90, 91, 98, 78, 74, 61, 35, 13, 14, and 9, and in consecutive subcortical WML severity categories 82, 98, 78, 75, 60, 35, 14, 13, and 10.
gle MRI scan, we cannot be sure that the decline in cognitive performance can be attributed to progression of WMLs. Serial MRI assessments, currently underway, are needed to clarify whether progression of periventricular WMLs is accompanied by an increase of the rate of cognitive decline and eventually in the development of dementia. If so, preventing or decreasing the progression of WMLs can be an important strategy in dementia prevention.

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References