Progression of Cerebral Small Vessel Disease in Relation to Risk Factors and Cognitive Consequences
Rotterdam Scan Study
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Background and Purpose—Cerebral white matter lesions and lacunar infarcts are small vessel disease-related lesions, which are associated with cognitive decline and dementia. We aimed to assess the relationship between risk factors, effect modifiers, and progression of these lesions. Furthermore, we studied the cognitive consequences of lesion progression.

Methods—Six hundred sixty-eight people, aged 60 to 90 years, underwent repeated MRI scanning and neuropsychological testing within 3-year follow-up. We rated incident lacunar infarcts and change in periventricular and subcortical white matter lesion severity with a semiquantitative scale. We assessed the relationships between age, sex, baseline lesion load, risk factors, lesion progression, and change in cognitive function by multivariate regression analyses and additional stratified analyses.

Results—Baseline lesion load, higher age, high blood pressure, and current smoking were independently associated with progression of white matter lesions. Women had more marked progression of subcortical white matter lesions and incident lacunar infarcts compared with men. Carotid atherosclerosis was associated with incident lacunar infarcts. Higher blood pressure did not contribute to lesion progression in people with already severe lesions at baseline nor in the very old. Lesion progression was associated with a paralleled decline in general cognitive function and in particular with a decreased information processing speed.

Conclusions—Higher age, female sex, cigarette smoking, elevated blood pressure, and baseline lesion load were associated with small vessel disease progression. Age and baseline lesion load influenced the risk relations with blood pressure. Progression of small vessel disease was related to a paralleled decline in cognitive function. (Stroke. 2008;39:2712-2719.)

Key Words: cerebral infarction ■ cognition impairment ■ MRI ■ population-based ■ prospective/cohort study ■ risk factors ■ white matter lesions

Cerebral white matter lesions and lacunar brain infarcts are caused by cerebral small vessel disease. Narrowing of the small vessel lumen and failure of cerebral autoregulation result in ischemic damage of the cerebral white and subcortical gray matter. These lesions are commonly observed on MRI scans of elderly people and are associated with an increased risk of stroke, dementia, and depression. Cross-sectional studies showed increased severity and a higher prevalence of white matter lesions and lacunar infarcts in older age. Hypertension is considered the main risk factor, but other cardiovascular risk factors may be related to these lesions as well. We earlier reported on risk factors for incident silent brain infarcts, which in the vast majority are lacunar infarcts, and on the association between the inflammation marker, C-reactive protein, and small vessel disease progression. Data on change of white matter lesions in community-dwelling people are very limited. The few studies in selected populations were too small to study modifiable risk factors for lesion progression. Next, the influence of a risk factor on disease progression may be different in early- and late-stage disease and in younger and older people. Presence of small vessel disease-related lesions on MRI predicts cognitive decline. Whether lesion progression also parallels this decline over time is less clear. Data on lesion progression, differential strength of risk factor relations, and the relation with cognitive function are essential in planning intervention studies.

We investigated, in a large population-based sample of elderly people, the association between baseline lesions, cardiovascular risk factors, and progression of cerebral white matter disease.
matter lesions and lacunar infarcts. Next, we studied whether age and the presence of white matter lesions and lacunar brain infarcts at baseline influenced these risk relations. Furthermore, we studied the relationship between lesion progression and change in cognitive function.

Methods

Study Population

The Rotterdam Scan Study is a prospective, population-based cohort study. We randomly selected participants aged 60 to 90 years in strata of age and sex from 2 large ongoing population-based studies. The characteristics of the 1077 nondemented participants have been described previously. Baseline examination in 1995 to 1996 comprised a structured interview, neuropsychological tests, physical examination, blood sampling, and a MRI scan of the brain. We monitored all participants throughout the study by ongoing review of medical records for death and major complications, including cognitive problems, dementia, stroke, and transient ischemic attack. In 1999 to 2000, all eligible participants were invited for a second MRI. Of the 1077 participants at baseline, 126 people were not eligible to participate in the second MRI examination (82 died, 19 had MRI contraindications, 19 were institutionalized, 3 moved abroad, and 3 could not be reached). In total, 668 of the 951 eligible persons underwent a second MRI in 1999 to 2000 with a mean interval of 3.4 years between the MRI examinations (response rate, 70%). The reasons for refusal to undergo the second MRI examination were claustrophobia developed at the baseline MRI (n = 98), too much trouble (n = 90), no interest (n = 77), and other reasons (n = 18).

MRI Scanning

In 1995 to 1996, we made axial T1-, T2-, and proton density-weighted cerebral MR scans on a 1.5-Tesla scanner (MR VISION, Siemens, or MR Gyroscan; Philips). In 1999 to 2000, participants underwent a second MRI on the MR VISION scanner using the same sequences.

White Matter Lesions

We considered white matter lesions (WMLs) to be in the periventricular region if they were directly adjacent to the ventricle; otherwise, we considered them subcortical. Baseline WML severity was scored on hard copy with a visual rating scale. We scored periventricular WMLs semiquantitatively in 3 regions (lesions adjacent to the frontal horns, the lateral walls, and the occipital horns of the lateral ventricle) resulting in a total score ranging from 0 to 9. For subcortical WMLs, we approximated a total volume based on number and size of lesions (range, 0 to 29.5 mL). We defined severe periventricular and subcortical white matter lesions as the upper quintile of their baseline distribution.

Two raters independently assessed progression of WML severity on digital T2-weighted and proton density-weighted images by direct scan comparison. Raters were blinded to scans being baseline or follow-up and to all clinical information. We scored differences in WML severity in the 3 periventricular regions of both hemispheres (periventricular score range, −6 to +6) and in the subcortical white matter of the 4 lobes of both hemispheres (subcortical score range, −8 to +8). The change rating showed good interobserver agreement (intraclass correlation coefficient, 0.75 to 0.79) and good to very good intraobserver agreement (intraclass correlation coefficient, 0.70 to 0.93). If raters disagreed 1 point or less on the scale, we used the mean of the ratings; otherwise, we held a consensus meeting. Adjudication by consensus meeting was required in 9% of the periventricular and 11% of the subcortical WML ratings. Progression was defined as an increase of 1 point or more between baseline and follow-up. We categorized progression into no progression (score <1), minor progression (score 1 to 2.5), and marked progression (score >2.5). Hyperintensities on proton density- and T2-weighted images around an incident infarct were not considered as progression of WMLs.

Cerebral Infarcts

The presence of brain infarcts was rated similarly at the baseline and follow-up MRI. We defined brain infarcts as areas of focal hyperintensity on T2-weighted images sized ≥3 mm. Areas of hyperintensity in the white matter also had to have corresponding prominent hypointensity on T1-weighted images to distinguish them from WMLs. We defined lacunar infarcts as infarcts sized 3 to 20 mm and located in the subcortical white matter or basal ganglia. Nonlacunar infarcts were excluded in the analyses of lacunar infarcts.

Cardiovascular Risk Factors

We measured blood pressure twice at the right arm with a random-zero sphygmomanometer and used the average. Smoking habits were classified as never, former, and current cigarette smoking. We considered diabetes mellitus to be present if the random glucose level was ≥11.1 mmol/L or if a person was taking oral antidiabetes medications or insulin. Nonfasting serum total cholesterol and high-density lipoprotein were determined. To determine plasma total homocysteine levels, we used a fluorescence polarization immunoassay on an IMx analyzer.

Partial arterial oxygen saturation was measured twice, with a pulse oximeter, and the averaged value was used (range, 86% to 99%). Participants underwent ultrasonography of both carotid arteries to obtain an atherosclerotic plaque score (range, 0 to 6) and an intima media thickness measurement. The presence of atrial fibrillation was assessed by MEANS interpretation of a 12-lead electrocardiogram. Apolipoprotein E genotyping was done on coded genomic DNA samples. The distribution of the apolipoprotein E genotype in this population was in Hardy-Weinberg equilibrium.

Cognitive Function

Participants underwent the following neuropsychological tests at the baseline examination: the Mini-Mental State Examination, the 15-word verbal learning test, the Stroop test, the Paper-and-Pencil Memory Scanning Task, and the Letter-Digit Substitution Task. We used alternative versions of the same neuropsychological tests at the second examination to minimize learning effects. For each participant, we calculated z-scores (individual test score minus mean test score divided by the SD) for the neuropsychological tests at baseline and at follow-up using the mean and SD of the baseline tests. We constructed compound scores for memory performance by averaging the z-scores of the total of 3 immediate recall trials and the delayed-recall trial of the 15-word verbal learning test. The compound score for psychomotor speed was the average of the z-scores for the reading subtask of the Stroop test, the one-letter subtask of the Paper-and-Pencil Memory Scanning Task, and the Letter–Digit Substitution Task. The compound score for global cognitive function was constructed by calculating the average of the z-scores for all these tests. Cognitive decline was calculated by subtracting the z-scores for memory performance, psychomotor speed, and global cognitive function at follow-up from the z-scores at baseline. Change in Mini-Mental State Examination score was calculated by subtracting follow-up from baseline scores.

Data Analysis

We used age- and sex-adjusted analysis of covariance to assess whether baseline risk factors differed between people with and without a second MRI assessment and calculated Spearman’s rho for correlation between periventricular and subcortical WML progression. We calculated WML progression percentages in strata of age (60 to 69 years, 70 to 79 years, and 80 to 90 years), baseline WML severity (in tertiles), and presence of lacunar infarcts at baseline. For the later 2 assessments, we used age- and sex-adjusted analysis of covariance. We used multivariate logistic and multinomial logistic regression analyses to study the association between risk factors incident lacunar infarcts and any, minor, and marked WML progression. People with a negative difference in WML severity over time
were added to the group of people with no progression. All analyses were adjusted for age and sex and additionally for cardiovascular risk factors. We considered baseline WML severity as an intermediate factor in the relation between risk factors and WML progression. Hence, we did not adjust for baseline lesion load. To assess whether the effect of risk factors on lesion progression was different in people with and without severe WMLs or prevalent lacunar infarcts at baseline, we did separate analyses in which we stratified on baseline lesion load. We also performed stratified analyses for the previously mentioned age strata. To formerly test for interaction, we added the interaction term to the regression models.

We estimated the association between the progression of WMLs and incident lacunar infarcts and change in cognitive function by multiple linear regression analysis adjusted for age, sex, and level of education. Incident nonlacunar infarcts were excluded from the analyses.

**Results**

People who underwent a second MRI were younger and less often used blood pressure-lowering medication than people who refused a second examination (Table 1). They were also younger, healthier, and more often female than people who were ineligible for a second MRI. Furthermore, they performed better on baseline cognitive function tests. The mean follow-up between the 2 MRI assessments was 3.4 years (SD, 0.2 years).

Twenty-seven percent of the people had any progression of periventricular WMLs and 32% had any progression of subcortical WMLs, whereas 39% had any progression of WMLs in either region. Spearman’s rho for the correlation between progression in the periventricular and subcortical region was 0.60 (P<0.001). Two people had minor regression of WMLs in the periventricular and 13 in the subcortical region. Marked subcortical white matter progression predominately consisted of growth and confluence of lesions, whereas minor progression mostly consisted of new small lesions. Ninety-three (14%) people had an incident infarct on follow-up MRI of which 81 (12%) were lacunar infarcts. Twelve (2%) people had a symptomatic infarct and 20 (3%) people experienced an incident transient ischemic attack in the period between the 2 MRI scans.

The extent of progression of both periventricular and subcortical WMLs was strongly related to age, baseline WML severity, and the presence of lacunar brain infarcts on baseline MRI (Figure). The proportion of both minor and marked WML progression was significantly larger in the strata of higher age, more severe baseline WML severity, and in those with presence of baseline lacunar infarcts (all probability values <0.001). None of the people without
Figure. Percentage periventricular and subcortical WML progression in age strata and in age- and sex-adjusted strata of baseline periventricular and subcortical WML severity (in tertiles) and for people with and without lacunar infarcts at baseline (age- and sex-adjusted differences in percentages of minor and marked progression between first and last stratum were all statistically significant, all probability values <0.001).
lesions at baseline and 3 people with only small punctate lesions (<3 mm) at baseline had marked subcortical WML progression.

Women had a higher risk of marked subcortical WML progression and incident lacunar infarcts than men (Table 2). Systolic and diastolic blood pressure was positively associated with WML progression, which remained after adjustment for use of blood pressure-lowering medication. Current, but not former, cigarette smoking was positively associated with marked WML progression. We did not observe a relation among atrial fibrillation, the extent of carotid atherosclerosis (carotid plaques and intima media thickness), homocysteine levels or oxygen saturation, and WML progression. Carotid atherosclerosis was associated with incident lacunar infarcts. The association of blood pressure and smoking with progression of WMLs was virtually unchanged after additional adjustment for other cardiovascular risk factors.

Subgroup analyses revealed that associations between blood pressure and WML progression and incident lacunar infarcts were strongest in the youngest age stratum (60 to 69 years) and in people without severe white matter lesions at baseline (Table 3). On the contrary, in the oldest people (80 to 90 years) and in people with severe WMLs or lacunar infarcts at baseline, blood pressure was not associated with lesion progression. The interactions between age and blood

### Table 2. Relationship Between Baseline Determinants and Progression of WMLs

<table>
<thead>
<tr>
<th></th>
<th>Periventricular WML Progression</th>
<th>Subcortical WML Progression</th>
<th>Incident Lacunar Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any OR (95% CI)</td>
<td>Marked OR (95% CI)</td>
<td>Any OR (95% CI)</td>
</tr>
<tr>
<td>Age per year</td>
<td>1.12 (1.09–1.15)</td>
<td>1.15 (1.11–1.20)</td>
<td>1.07 (1.04–1.09)</td>
</tr>
<tr>
<td>Sex, women</td>
<td>1.21 (0.84–1.74)</td>
<td>1.58 (0.89–2.73)</td>
<td>1.09 (0.78–1.52)</td>
</tr>
<tr>
<td>Systolic blood pressure per SD</td>
<td>1.23 (1.02–1.48)</td>
<td>1.21 (0.90–1.61)</td>
<td>1.18 (0.99–1.40)</td>
</tr>
<tr>
<td>Diastolic blood pressure per SD</td>
<td>1.32 (1.10–1.59)</td>
<td>1.38 (1.04–1.84)</td>
<td>1.21 (1.03–1.44)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.80 (1.10–2.95)</td>
<td>2.63 (1.27–5.41)</td>
<td>1.49 (0.95–2.34)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.79 (0.35–1.78)</td>
<td>1.38 (0.48–3.95)</td>
<td>0.61 (0.28–1.33)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.66 (0.21–2.10)</td>
<td>0.31 (0.03–2.71)</td>
<td>0.61 (0.20–1.82)</td>
</tr>
<tr>
<td>Cholesterol per SD</td>
<td>0.90 (0.74–1.08)</td>
<td>0.94 (0.71–1.26)</td>
<td>0.93 (0.78–1.11)</td>
</tr>
<tr>
<td>High-density lipoprotein per SD</td>
<td>1.00 (0.83–1.21)</td>
<td>1.12 (0.84–1.47)</td>
<td>1.13 (0.95–1.35)</td>
</tr>
<tr>
<td>Homocysteine per SD</td>
<td>1.10 (0.89–1.35)</td>
<td>0.98 (0.73–1.31)</td>
<td>0.95 (0.80–1.14)</td>
</tr>
<tr>
<td>Oxygen saturation per SD</td>
<td>0.87 (0.72–1.06)</td>
<td>0.92 (0.69–1.24)</td>
<td>1.05 (0.88–1.25)</td>
</tr>
<tr>
<td>Carotid intima media thickness per SD</td>
<td>1.00 (0.82–1.23)</td>
<td>1.02 (0.85–1.22)</td>
<td>1.02 (0.85–1.22)</td>
</tr>
<tr>
<td>Carotid plaques (range, 0–6)</td>
<td>1.09 (0.97–1.24)</td>
<td>0.98 (0.81–1.19)</td>
<td>1.11 (0.99–1.25)</td>
</tr>
<tr>
<td>Apolipoprotein e4 carrier</td>
<td>0.91 (0.59–1.40)</td>
<td>1.07 (0.55–2.07)</td>
<td>1.07 (0.73–1.58)</td>
</tr>
</tbody>
</table>

Age- and sex-adjusted ORs with no progression as the reference for both any and marked progression (with 95% CIs).

### Table 3. Relationship Between Blood Pressure and Progression of WMLs Stratified on Age and Baseline White Matter Severity or Presence of a Lacunar Infarct

<table>
<thead>
<tr>
<th></th>
<th>ORs for Any Subcortical WML Progression (95% CI)</th>
<th>ORs for Any Periventricular WML Progression (95% CI)</th>
<th>ORs for Incident Lacunar Infarcts (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per SD Increase in SBP per SD Increase in DBP</td>
<td>per SD Increase in SBP per SD Increase in DBP</td>
<td>per SD Increase in SBP per SD Increase in DBP</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69 years</td>
<td>1.48 (1.10–1.99)</td>
<td>1.45 (1.07–1.96)</td>
<td>1.30 (1.01–1.67)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>1.27 (0.96–1.68)</td>
<td>1.37 (1.03–1.84)</td>
<td>1.16 (0.88–1.52)</td>
</tr>
<tr>
<td>80–90 years</td>
<td>0.69 (0.42–1.13)</td>
<td>0.99 (0.65–1.51)</td>
<td>0.91 (0.56–1.45)</td>
</tr>
<tr>
<td>Baseline lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No severe WML/LI</td>
<td>1.25 (0.99–1.59)</td>
<td>1.36 (1.08–1.71)</td>
<td>1.12 (0.90–1.39)</td>
</tr>
<tr>
<td>Severe WML/LI</td>
<td>0.98 (0.67–1.44)</td>
<td>0.89 (0.60–1.32)</td>
<td>0.91 (0.62–1.35)</td>
</tr>
</tbody>
</table>

Age- and sex-adjusted ORs with no progression as the reference (with 95% CIs).

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; LI, lacunar infarct.
pressure and between baseline lesions and blood pressure in relation to lesion progression were, however, not statistically significant.

Periventricular WML progression and incident lacunar infarcts were associated with a decline in general cognitive function and in particular information processing speed, whereas no relationship between lesion progression and change in memory function was observed (Table 4). Only periventricular WML progression was associated with a decline in Mini-Mental State Examination score.

Discussion

We found in a population-based sample of non-demented people between 60 and 90 years that older age, female sex, higher blood pressure, current cigarette smoking, and the presence of severe WMLs and lacunar brain infarcts at baseline were associated with progression of WMLs. Baseline carotid atherosclerosis was related to incident lacunar infarcts. These associations were independent of other cardiovascular risk factors. In people with already severe small vessel disease at baseline and in those in the oldest age category, higher blood pressure seemed no longer related to lacunar brain infarcts at baseline are strongly associated with progression of WMLs.4 In the Austrian Stroke Prevention Study, 18% of the participants had any and 8% had marked progression within 3 years of follow-up.9 The lower proportion of progression of WMLs in that study compared with our findings could be explained by the exclusion of people with cerebrovascular disease and the 10-year lower mean age of the participants. The progression rate in the Cardiovascular Health Study was with 28% in 5 years, comparable with our findings.

In cross-sectional studies, older age and higher blood pressure, in particular diastolic blood pressure, were strongly associated with WML severity.6,22,23 Furthermore, women tended to have more severe white matter lesions.24 We observed that these risk factors are also associated with progression of WMLs. The Austrian Stroke Prevention Study and the Cardiovascular Health Study reported the same associations with age and diastolic blood pressure.9,11 In agreement with the latter study, we found that current cigarette smoking was associated with marked WML progression.

Our data confirm that WML severity and presence of lacunar brain infarcts at baseline are strongly associated with lesion progression.9,11,25 The association between lacunar brain infarcts and progression of WMLs can be explained by a shared exposure to risk factors and susceptibility for these factors, resulting in a common pathological substrate.7 Base-
line WMLs and lacunar infarcts probably reflect cerebral small vessel disease and related chronic cerebral ischemia. We hypothesize that just longer duration of exposure to small vessel disease could, even without additional vessel damage, result in progression of WMLs and lacunar infarcts.

We found that in the oldest people and in people with severe WMLs at baseline, higher blood pressure was not a risk factor for WML progression any more. This is in agreement with our earlier finding that blood pressure is not related to incident silent brain infarcts in people with prevalent silent brain infarcts and with the results from the Cardiovascular Health Study.7,11,26 In a subgroup of people with evident small vessel disease, high blood pressure may lead to progression of small vessel damage on the one hand, but may be essential to maintain adequate cerebral perfusion in a state of impaired autoregulation on the other. These potential opposite roles of blood pressure might explain the absence of a risk relation between blood pressure and WML progression in very old people and in those with already severe lesions at baseline. A different explanation of the negative results in older people and people with vascular lesions at baseline could be that cardiovascular risk factors do not further discriminate within a group of people already at high risk.

We previously reported on the cross-sectional association among atrial fibrillation,27 carotid atherosclerosis,18 homocysteine levels,16 oxygen saturation,17 and WMLs. We did not observe an association between these factors and progression of WMLs. This could be explained by selective follow-up as noted earlier. Alternative explanations for these distinct findings are the smaller samples size and the possibility that baseline WML distribution is a more robust measure of small vessel disease because it reflects accumulation of lesions over a longer period of time than the follow-up time. The observation that WML progression and incident lacunar infarct do not only predict cognitive decline, but also parallel it over time, even stronger suggests that these lesions play a causative role. The relationship between progression of small vessel disease and change in cognitive function is complex. A different kind of co-occurring lesion at a different anatomic location interacts in affecting different cognitive domains. Despite this complexity, the relationship between periventricular WML progression and decrease in psychomotor speed seems robust given the comparable results in the Cardiovascular Health Study and the PROSPER trial cohort.10,11,28 Our finding that memory performance improved at the second examination may be explained by a learning effect that does not effect psychomotor speed tests.

Because WML progression is strongest in the oldest people and in those with already severe lesions at baseline, it seems to be a chronic disorder that accelerates over time. We hypothesize that at time of this acceleration, the effect of traditional treatable risk factors attenuates and factors like inflammation and chronic hypoperfusion take over.8 Future studies aimed to slow cognitive decline by prevention of cerebral small vessel disease-related brain damage should evaluate the effect of rigorous treatment of high blood pressure, taking into account the potential weak or even negative effect in the very old and in those already at a severe stage of small vessel disease.

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**Disclosures**

None.

**References**

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