Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: Progression of MR Abnormalities in Prospective 7-year Follow-up Study

Purpose: To prospectively investigate the patterns and rates of progression of magnetic resonance (MR) imaging abnormalities in a well-documented cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) cohort 7 years after baseline and to identify the prognostic factors that determine the rates and patterns of this progression.

Materials and Methods: The local ethics committee approved the study, and informed consent was obtained from all participants. From 12 unrelated families, 25 patients who were NOTCH3 mutation carriers and 13 who were non–mutation carriers were examined clinically and with standardized MR imaging at baseline and after 7 years. The progression of white matter hyperintensities (WMHs), lacunar infarcts, microbleeding, and brain volume loss was measured semiquantitatively. Correlation testing and group comparison testing were performed to identify the risk factors associated with increased progression of CADASIL-related MR abnormalities.

Results: Compared with the non–mutation carriers, the mutation carriers showed significant increases in numbers of lacunar infarct ($P < .01$), WMH ($P < .01$), and microbleed ($P < .05$) lesions but no increased loss of brain volume. The distributions of new WMHs and new lacunar infarcts at follow-up were similar to the distributions of these abnormalities at baseline. High WMH ($P < .05$), lacunar infarct ($P < .01$), and microbleed ($P < .01$) lesion loads at baseline—but not cardiovascular risk factors—were associated with faster progression of these abnormalities.

Conclusion: Patients with CADASIL who have a high MR abnormality lesion load at baseline are at risk for faster progression of MR abnormalities.

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy caused by mutations of the NOTCH3 gene. The microvascular changes are systemic, but the brunt of the abnormality affects the cerebral vasculature (1). Clinical hallmarks are recurrent stroke, cognitive decline, migraine with aura (in up to 40% of patients), and mood disorders (in up to 30% of patients) (2). Magnetic resonance (MR) imaging invariably reveals characteristic areas of white matter hyperintensity (WMH) with or without subcortical lacunar lesions (3), lacunar infarcts, and microbleeds in both symptomatic and asymptomatic adult human mutation carriers (4,5).

The results of various studies have established that MR imaging abnormalities in CADASIL are associated with clinical disease severity. Lacunar infarct and global brain atrophy were found to be associated with cognitive dysfunction (6,7), and WMH, lacunar infarct, microbleeding, and brain atrophy were found to be associated with physical disability (7–10). Cross-sectional studies have shown that the MR imaging abnormalities in CADASIL are also associated with cardiovascular risk factors, such as systolic blood pressure, hemoglobin A1c level, sex, and age (4,11). The different MR imaging abnormalities are interrelated: The presence of a large number of microbleeds is associated with higher WMH and lacunar infarct volumes, whereas high lacunar infarct volume is associated with global brain atrophy (10,12). Because most studies for evaluating MR imaging lesions in CADASIL are cross-sectional, little is known about the long-term progression of MR imaging abnormalities or the prognostic risk factors associated with this progression. Two previously performed longitudinal MR imaging studies involved follow-ups of 2 years or less, without specific assessment of the prognostic risk factors (8,13). The aim of this study was to investigate the patterns and rates of progression of MR imaging abnormalities in a well-documented CADASIL cohort 7 years after baseline and to identify the prognostic factors that determine the rates and patterns of this progression.

### Materials and Methods

#### Patients

Participants were recruited from a cross-sectional cohort of patients with CADASIL who were examined at baseline in 1999 and 2000 (4). These patients, from 15 unrelated families, included 40 symptomatic and asymptomatic NOTCH3 gene mutation carriers and 22 non–mutation carriers. All participants were invited to undergo follow-up examinations. Interval deaths and reasons for not participating in the follow-up were recorded. Informed consent was obtained from the participants or from their family member(s) if the participant was unable to provide it. Exclusion criteria were age younger than 18 years at baseline, inability to provide informed consent at baseline, and/or any contraindication to MR imaging at baseline or follow-up. A total of 38 members from 12 unrelated families—25 mutation carriers and 13 non–mutation carriers—participated in the follow-up study. The non–mutation carriers served as control subjects because of the genetic and environmental backgrounds that they partially shared with mutation carriers from the same family.

Approval for the study was obtained from the local medical ethics committee of Leiden University Medical Center.

The follow-up examinations were performed between November 2006 and September 2007. We obtained full medical histories of all participants and obtained medical records from their physicians and general practitioners. The following cardiovascular risk factors were determined: cigarette smoking history during the follow-up interval (in pack-years); history of hypertension, hypercholesterolemia, or diabetes mellitus; and migraine at baseline. Body mass index and presence or absence of apolipoprotein E genotype e4 were also determined at baseline. Clinical and radiologic examinations were performed with blinding to the NOTCH3 mutation status.

#### MR Imaging

**Image acquisition.**—The same MR imaging protocol and the same 1.5-T MR sys-

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**Abbreviations:**
- ANCOVA = analysis of covariance
- CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- CSF = cerebrospinal fluid
- WMH = white matter hyperintensity

**Author contributions:**
- Guarantors of integrity of entire study, M.K.L., S.A.J.L.O., R.v.d.B., J.v.d.G.; and manuscript editing, all authors
- Authors stated no financial relationship to disclose.

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**Implication for Patient Care**

- Since patients with a high MR imaging lesion load are at risk for faster progression of the disease, they may require more frequent clinical monitoring and MR imaging follow-up, whereas patients with a low lesion load at MR imaging may require less frequent monitoring.
system (Gyroscan Intera ACS-NT, Philips Medical Systems, Best, the Netherlands) were used at baseline and follow-up. Conventional T1-weighted spin-echo (600/20 [repetition time msec/echo time msec], 6-mm section thickness with 0.6-mm intersection gap, 256 × 205 matrix, 220 × 165-mm field of view), T2-weighted dual spin-echo (3000/27, 120; 3-mm section thickness without intersection gap: 256 × 205 matrix; 220 × 220-mm field of view), and fluid-attenuated inversion-recovery (8000/100/2000 [repetition time msec/echo time msec/inversion time msec], 3-mm section thickness without intersection gap, 256 × 205 matrix, 220 × 176-mm field of view) MR images were obtained. To detect cerebral microbleeding, T2*-weighted gradient-echo echo-planar imaging (2598/48, 6-mm section thickness with 0.6-mm intersection gap, 256 × 192 matrix, echo-planar imaging factor of 25) was performed. All images were acquired in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum.

Image postprocessing.—For volumetric MR imaging measurements of the brain parenchyma, cerebrospinal fluid (CSF), and WMHs, we used locally developed semiautomated segmentation software (Software for NeuroImage Processing in Experimental Research [SNIPER]; Neuro-Image Processing Group, Leiden University Medical Center, Leiden, the Netherlands) that combines knowledge-based fuzzy clustering and region-growing techniques (14). This software has been validated for lesion segmentation in elderly persons with WMHs. The WMHs in elderly individuals resemble the WMHs in patients with CADASIL (14). Measurements were performed on dual spin-echo and fluid-attenuated inversion-recovery images.

The intracranial volume was determined after skull stripping. The brain parenchyma and CSF were then segmented separately. Normalized brain volume, expressed as a percentage, was defined as the brain parenchyma volume relative to the total intracranial volume. We also divided the CSF volume into ventricular CSF volume and peripher-
testing for the other variables.

Covariance analysis of means was used to analyze continuous variables. Family identification number was included as a covariate in these tests.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mutation Carriers (n = 25)</th>
<th>Non–Mutation Carriers (n = 13)</th>
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<tr>
<td>No. of male/female patients</td>
<td>11/14</td>
<td>7/6</td>
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<tr>
<td>Age (y)†</td>
<td>42.2 ± 10</td>
<td>36.7 ± 8</td>
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<tr>
<td>Mean age of male patients‡</td>
<td>42.3 (21–55)</td>
<td>32.0 (23–44)</td>
</tr>
<tr>
<td>Mean age of female patients‡</td>
<td>42.2 (22–51)</td>
<td>42.2 (35–48)</td>
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<td>Cardiovascular risk factors</td>
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<td>Hypertension</td>
<td>2 (8)</td>
<td>3 (23)</td>
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<tr>
<td>Smoking history during follow-up interval (mean no. of pack-years)‡</td>
<td>0.8 (0–7)</td>
<td>3.4 (0–12)</td>
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<td>Hypercholesterolemia</td>
<td>10 (40)</td>
<td>2 (15)</td>
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<tr>
<td>Diabetes</td>
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<td>0</td>
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<tr>
<td>Body mass index*</td>
<td>26.2 ± 2.9</td>
<td>25.5 ± 5.9</td>
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<tr>
<td>Migraine</td>
<td>9 (36)</td>
<td>3 (23)</td>
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<tr>
<td>Apolipoprotein E genotype ‡</td>
<td>5 (23)</td>
<td>3 (27)</td>
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</table>

Note.—Unless otherwise noted, data are numbers of patients, with percentages in parentheses. P > .05 for all comparisons between NOTCH3 mutation carriers and non–mutation carriers. Covariance analysis of means was used to analyze continuous variables: age and body mass index. Covariance analysis based on ranks was used to analyze the continuous variable smoking history during follow-up interval. Cochran-Mantel-Haenszel χ² testing was used to test categorical variables. Family identification number was included as a categorical covariate in these tests.

* Mean value ± standard deviation.
† Numbers in parentheses are ranges.
‡ Apolipoprotein E genotype status was not available for three mutation carriers and two noncarriers, so these percentages are based on 22 mutation carriers and 11 non–mutation carriers.

Table 2

<table>
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<th>MR Imaging Characteristic</th>
<th>Mutation Carriers (n = 25)</th>
<th>Non–Mutation Carriers (n = 13)</th>
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<td>WMH volume (%)*</td>
<td>5.0 ± 3.9</td>
<td>7.4 ± 5.3</td>
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<td>Mean no. of lacunar infarcts‡</td>
<td>6.2 (0–27)</td>
<td>9.9 (0–36)</td>
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<td>Mean no. of microbleeds§</td>
<td>1.6 (0–35)</td>
<td>3.2 (0–40)</td>
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<td>Normalized brain volume (%)*</td>
<td>82.6 ± 2.9</td>
<td>81.8 ± 3.2</td>
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<td>Ventricular volume (%)*</td>
<td>2.5 ± 1.0</td>
<td>2.9 ± 1.4</td>
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<td>Peripheral CSF volume (%)*</td>
<td>14.9 ± 3.0</td>
<td>15.2 ± 2.9</td>
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<td>Subcortical lacunar lesions Yes</td>
<td>11†</td>
<td>13</td>
</tr>
<tr>
<td>Subcortical lacunar lesions No</td>
<td>14†</td>
<td>12</td>
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Note.—The following analyses were performed for mutation carrier versus non–mutation carrier comparisons: ANCOVA based on ranks, with family identification number as a categorical covariate for WMH volume, number of lacunar infarcts, and number of microbleeds; McNemar testing for subcortical lacunar lesions. The following analyses were performed for baseline versus follow-up comparisons: paired-samples Wilcoxon testing for WMH volume, number of lacunar infarcts, and number of microbleeds; McNemar testing for subcortical lacunar lesions; and paired-samples t testing for the other variables.

* Mean value ± standard deviation.
† P < .01 for difference between mutation carrier and non–mutation carrier values at baseline.
‡ P < .01 for difference between baseline and follow-up values.
§ Numbers in parentheses are ranges.
† P < .05 for difference between mutation carrier and non–mutation carrier values at baseline.
* P < .05 for difference between baseline and follow-up values.

maps to produce a visual map of the 7-year differences in WMHs and lacunar infarcts.

Statistical Analyses

Statistical analyses were performed by using the SPSS-14 statistical software package (SPSS, Chicago, Ill). Differences in demographic characteristics, cardiovascular risk factors, and MR imaging parameters between the NOTCH3 mutation carriers and the non–mutation carriers were analyzed by using parametric and nonparametric analyses of covariance (ANCOVA) for continuous variables and Cochran-Mantel-Haenszel χ² tests for categorical variables. To account for sources of correlation among observations within the same family, family identification number was used as a categorical covariate. In the comparisons of brain volume, ventricular volume, and peripheral CSF volume, age was used as a covariate to correct for possible age-related differences between the mutation carriers and non–mutation carriers. To identify the possible effects of selection bias on the study population, we also compared the baseline MR imaging parameters between the mutation carriers who did and those who did not provide follow-up data by using parametric and nonparametric ANCOVA, with family identification number as a categorical covariate.

To determine whether the distributions of WMHs and lacunar infarcts at baseline were age related, we used Spearman rank correlation coefficients for age with the WMH volume percentage and the lacunar infarct count in each brain sublocation. Changes in MR imaging parameters between baseline and follow-up were analyzed by using paired t, paired Wilcoxon, and McNemar tests. To determine whether the distributions of new WMHs and lacunar infarcts were different from the distributions of these abnormalities at baseline, we performed conditional logistic regression testing of lacunar infarct distributions with subject identification number as a covariate and performed mixed-model ANCOVA of the percentage increases in WMHs between the different brain regions with subject identification number as a random classification factor. Changes in MR imaging
scores were correlated with baseline MR imaging scores, demographic variables, disease durations, and cardiovascular risk factors by using Spearman rank correlation coefficient, Pearson correlation coefficient, Student t test, and Mann-Whitney U test analyses. The Simes step up test (16), a modified Bonferroni correction, was applied to this multiple-correlation testing, which was based on a total of 68 statistical tests. Results were deemed to be significant at \( P < .05 \).

**Results**

**Patients**

Of the 62 original participants, seven died during the follow-up period, and 38 of the 55 remaining participants consented to participate in the follow-up study. Reasons for not participating were severe disease \(( n = 3 \) ), disease-related immobility \(( n = 2 \) ), hospital anxiety \(( n = 2 \) ), and lack of interest or motivation \(( n = 8 \) ). Two individuals did not provide a reason for their nonparticipation. Of the total of 24 subjects who did not participate, 15 were NOTCH3 mutation carriers. ANCOVA revealed that these mutation carriers had significantly more lacunar infarcts \(( P = .001 \) ), microbleeds \(( P = .03 \) ), and WMHs \(( P < .001 \) ) at baseline than did the mutation carriers who participated in the follow-up study.

Of the 38 participants in the follow-up study, 25 were NOTCH3 mutation carriers. The average time between the baseline and follow-up examinations was 7.1 years \(( \text{range, 6.4–7.7 years} \) ). Eight mutation carriers were asymptomatic at the baseline visit. The disease durations in the other mutation carriers were less than 5 years \(( \text{five carriers} \) ), 5–10 years \(( \text{five carriers} \) ), and 10–21 years \(( \text{seven carriers} \) ). There were no marked differences in sex, age, or cardiovascular risk factors between the mutation carriers and the non–mutation carriers \(( \text{Table 1} \) ).

**MR Imaging Characteristics at Baseline and Follow-up**

In the mutation carriers, the numbers of lacunar infarcts \(( P < .01 \) ), WMHs \(( P < .01 \) ), and microbleeds \(( P < .05 \) ) increased significantly between baseline and follow-up \(( \text{Table 2} \) ). The non–muta-
tion carriers had no lacunar infarcts or microbleeds and no substantial amounts of WMHs at baseline or follow-up. At baseline, no significant differences in normalized brain volume, ventricular volume, or peripheral CSF volume were found between the mutation carriers and the non–mutation carriers. At follow-up, the mutation carriers had significant increases in ventricular volume ($P < .01$) and significant decreases in normalized brain volume ($P < .05$). At follow-up, the non–mutation carriers had decreases in normalized brain volume similar to those of the mutation carriers but no significant increases in ventricular volume.

**Distribution of WMHs and Lacunar Infarcts**

Figures 1 and 2 show the distributions of WMHs and lacunar infarcts that were present at baseline (Fig 1a) compared with the WMHs and lacunar infarcts that were new at follow-up (Fig 1b). At baseline, the highest load of WMH lesions was found in the anterior temporal lobes and in the deep white matter of the frontal and parietal lobes. The occipital lobes were relatively spared, and virtually no lesions were found in the cerebellum. Sixty percent ($872 \text{ mL}/1446 \text{ mL}$) of the WMHs were located in the frontal lobes; 38% ($546 \text{ mL}/1446 \text{ mL}$), in the temporal and parietal lobes; and less than 2% ($28 \text{ mL}/1446 \text{ mL}$), in the occipital lobe and brainstem (Fig 2a). Correlation testing revealed that this distribution of WMHs was independent of age. Figure 1b shows that the newly developed WMHs were distributed diffusely in all locations that were affected at baseline. Likewise, Figure 2b shows that the distribution of new WMHs between the brain lobes was virtually identical to the distribution of WMHs at baseline. These findings were confirmed at mixed-model ANCOVA testing.

Figure 2c shows that the distribution of lacunar infarcts at baseline was different from the WMH distribution at baseline. The majority of lacunar infarcts were located in the basal ganglia and surrounding white matter areas. Figures 1a and 2a show that in contrast to the

**Table 3**

<table>
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<tr>
<th>Baseline MR Characteristic</th>
<th>WMH Increase</th>
<th>Lacunar Infarct Increase</th>
<th>Microbleed Increase</th>
<th>Normalized Brain Volume Increase</th>
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</thead>
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<tr>
<td>WMH volume</td>
<td>0.56*</td>
<td>0.66†</td>
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<td>NS</td>
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<tr>
<td>No. of lacunar infarcts</td>
<td>0.54*</td>
<td>0.72†</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>No. of microbleeds</td>
<td>NS</td>
<td>NS</td>
<td>0.70†</td>
<td>NS</td>
</tr>
<tr>
<td>Normalized brain volume</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Ventricular volume</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<td>Peripheral CSF volume</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Presence or absence of subcortical lacunar lesions</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Two-sample t tests and Mann-Whitney U tests were used to analyze correlations with subcortical lacunar lesions. Pearson correlation coefficient analysis was used to analyze correlations between increase in normalized brain volume and normalized brain volume, ventricular volume, and peripheral CSF volume. Spearman rank correlation coefficient analysis was used to analyze the other correlations. Thus, all numeric values are Spearman rank correlation coefficients. NS = not significant ($P > .05$).

* $P < .05$.
† $P < .01$ (corrected for multiple comparisons).
distribution of WMHs, lacunar infarcts were relatively sparse in the anterior parts of the temporal lobes. Correlation testing of the lacunar infarct distribution at baseline revealed that higher age was associated with significantly more infarcts in the parietal lobe (P = .03). The pie chart illustrating the distribution of new lacunar infarcts revealed that the percentage of parietally located lacunar infarcts was 11% higher than that at baseline. However, conditional logistic regression testing of the distribution of lacunar infarcts did not reveal any significant differences in distribution between the baseline and new infarcts.

Prognostic Risk Factors for Progression of MR Imaging Abnormalities

Neither age, sex, disease duration, nor any cardiovascular risk factor proved to be associated with the progression of any MR imaging parameter (Table 3). A high load of WMH (P < .05), lacunar infarct (P < .001), and/or microbleed (P < .001) lesions at baseline was associated with a faster progression of these abnormalities. WMH volume at baseline enabled the prediction of lacunar infarct progression at follow-up (P < .01), and, conversely, lacunar infarct lesion load at baseline predicted the progression of WMH volume at follow-up (P < .05). Subcortical lacunar lesions, normalized brain volume, ventricular volume, and peripheral CSF volume had no prognostic value in relation to any of the MR imaging parameters. Also, normalized brain volume at follow-up was not associated with any of the MR imaging parameters at baseline.

Discussion

The results of this longitudinal study show that lacunar infarcts, WMHs, and microbleeds are progressive in patients with CADASIL and that a higher load of these lesions at baseline is predictive of faster lesion progression at follow-up. The results also demonstrate that the progression of WMHs and lacunar infarcts has a distribution similar to the distribution of these parameters at baseline. While age and cardiovascular risk factor profile had no predictive value in terms of lesion progression, lesion load at baseline had predictive value in terms of lesion progression at follow-up: The higher the lesion load was at baseline, the greater the increase in number or extension of new lesions was at follow-up.

The longitudinal increase and distribution pattern of lacunar infarcts and microbleeds have not been well described in the literature. The increase in WMHs that we observed partially confirms the findings of the 2-year follow-up study of Peters et al (9). We also found WMH volume at baseline to be predictive of the progression of both WMH volume and lacunar infarct lesion load at follow-up. Likewise, lacunar infarct lesion load at baseline was predictive of the progression of both lacunar infarct lesion load and WMH volume at follow-up. Microbleed count at baseline, however, was predictive of its own progression only and not of the progression of either WMH volume or lacunar infarct lesion load. The finding that progression of lacunar infarcts and progression of WMHs seem to be closely associated, but progression of microbleeds does not seem to be related to the progression of either WMH volume or lacunar infarct lesion load. The finding that progression of lacunar infarcts and progression of WMHs seem to be closely associated, but progression of microbleeds does not seem to be related to the progression of either WMH volume or lacunar infarct lesion load. The finding that the vascular origin of WMHs and lacunar infarcts may be different from that of microbleeds in patients with CADASIL, even though these parameters are related to the same underlying disease. WMHs and lacunar infarcts are considered to be of ischemic origin, whereas microbleeds may result from vessel wall damage independent of ischemia, as suggested by the autopsy findings in a study of microbleeds in CADASIL (17). Another finding that supports a distinct vascular origin of microbleeds is the reported different distribution of microbleeds compared with that of WMHs and lacunar infarcts (10).

Our finding that the rate of brain volume loss is equal between mutation carriers and non–mutation carriers is in contrast to findings in the study of Peters et al, which suggest that global brain atrophy has an important role in CADASIL (9). It is possible that our statistical analysis of whole brain volume was limited by the smaller sample size. However, an important advantage of our study is that we compared rates of brain volume loss progression in patients who had CADASIL with those in age-matched unaffected family members, whereas Peters et al compared atrophy rates in patients who had CADASIL with data reported in the literature. Our results suggest that brain atrophy is not part of the MR imaging spectrum of CADASIL.

This study had limitations. An overall drawback was the relatively small number of patients, which may have limited the statistical power of some of the correlation calculations. Another limitation was the group of 24 participants who were lost to follow-up, who included mutation carriers who died or were immobile because of severe disease. Statistical analyses revealed that the mutation carriers who were lost to follow-up had significantly more MR imaging abnormalities at baseline than did the mutation carriers who participated in the follow-up study. Therefore, our results are based primarily on the follow-up of patients who were relatively healthy at baseline, and, thus, they may not have provided an unbiased reflection of the patients with CADASIL in the original cohort. The strength of this study lies in its longitudinal design.

Finally, our findings have important implications for the counseling and treatment management of patients with CADASIL. A patient with a high MR imaging lesion load is at risk for faster progression of the disease and thus may require more frequent clinical monitoring and MR imaging follow-up, whereas a patient with a low lesion load at MR imaging probably has a relatively good prognosis for the next 5–10 years and may require less frequent monitoring. Patients with lacunar infarcts in particular should be monitored closely because lacunar infarcts are associated with disability and cognitive decline (6,7).

References


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