Diffusion Magnetic Resonance Histograms as a Surrogate Marker and Predictor of Disease Progression in CADASIL

A Two-Year Follow-Up Study

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Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebral small vessel disease caused by mutations in the NOTCH3 gene. MRI is sensitive in detecting preclinical involvement and changes over time. However, little is known about correlations between MRI metrics and clinical measures on a longitudinal scale. In this study, we assessed the role of quantitative MRI (T2-lesion volume and diffusion tensor imaging [DTI]–derived metrics) in monitoring and predicting disease progression.

Methods—Sixty-two CADASIL subjects were followed prospectively over a period of 26.3±1.2 months. Dual-echo scans, DTI scans, and clinical scales were obtained at baseline and at follow-up. T2-lesion volumes were determined quantitatively, and histograms of mean diffusivity (MD) were produced.

Results—At follow-up, T2-lesion volumes and MD histogram metrics had changed significantly (all P<0.01). Lesion volumes and average MD correlated with clinical scores at baseline. Changes of average MD correlated with changes of the Rankin score, the National Institutes of Health Stroke Scale score, and the structured interview for the diagnosis of Alzheimer dementia and multiinfarct dementia score (all P<0.01). On multivariate analysis, average MD and systolic blood pressure at baseline were predictors of changes of average MD during follow-up. Moreover, average MD was the main predictor of clinical progression. Sample size estimates showed that the number of individuals required to detect a treatment effect in an interventional trial may be reduced when using MD histograms as an end point.

Conclusions—This study establishes correlations between changes of DTI histogram metrics and clinical measures over time. DTI histograms may be used as an adjunct outcome measure in future therapeutic trials. Moreover, DTI histogram metrics predict disease progression in CADASIL. (Stroke. 2005;36:2559-2565.)

Key Words: CADASIL ■ Notch3 ■ stroke ■ MRI ■ MR-histogram

Cerebral small vessel disease (SVD) is a major cause of disability and dementia in elderly people.1 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic variant of SVD caused by NOTCH3 mutations. Recurrent strokes and progressive cognitive decline are the main clinical manifestations.2–4 In view of the poor prognosis4 and the lack of an efficient treatment, there is demand for explorative trials. Yet, sample size calculations have shown that the number of patients needed to demonstrate a significant treatment effect is large when using clinical end points.5

Conventional MRI is sensitive in detecting preclinical involvement and has been recognized as an important diagnostic tool in CADASIL.6–7 Moreover, the volume of T2-visible lesions was found to correlate with clinical scales in cross-sectional studies.8 However, without longitudinal data, the role of the T2-lesion volume in monitoring or predicting disease progression remains unknown.

Diffusion tensor imaging (DTI) detects ultrastructural tissue damage even in areas that appear normal on a conventional MRI.9,10 Quantitative measures of a large proportion of the brain can be obtained by means of histograms of the mean diffusivity (MD). In a recent pilot study in 14 CADASIL subjects, average values of MD histograms were more sensitive than clinical scales in detecting changes over time.11 Moreover, increases in average MD were most pronounced in the small number of patients who showed increases in disability during follow-up. However, the study was not sufficiently powered to formally address correlations between DTI and clinical measures on a longitudinal scale.

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Correlations with clinical measures over time are one of the preconditions for establishing surrogacy of a biological marker in therapeutic trials. Establishing MRI as a surrogate marker for clinical progression would be of great interest, because MRI end points might reduce the number of patients needed to demonstrate a treatment effect. Surrogate markers might additionally be suited to identify risk factors for disease progression and, thus, possible targets for therapy.

The aim of this study was as follows: (1) to assess the role of quantitative MRI in monitoring disease progression; (2) to investigate correlations with clinical measures both cross-sectionally and on a longitudinal scale; (3) to provide sample size calculations for MRI end points; and (4) to identify prognostic markers and possible risk factors for disease progression. To address these issues, we prospectively followed a large cohort of CADASIL patients by quantitative MRI and standardized clinical scales.

Methods

Subjects

Study participants were recruited as part of a larger study. In the present study, we included all of the individuals (29 men, 35 women, age 44.9 ± 9.9 years) with proven CADASIL in whom DTI had been performed. None of the participants had had a stroke within the 3 months preceding inclusion into the study. We also studied 7 healthy controls (age 42.4 ± 9.1 years).

Design

All of the subjects were examined twice by a trained neurologist, at baseline and at the end of the follow-up period. At both time points, patients were assessed using the following scales: the modified Rankin scale, the Barthel index, the National Institutes of Health Stroke Scale, the Mattis dementia rating scale, and the structured interview for the diagnosis of Alzheimer dementia and multi-infarct dementia (SIDAM). Hypertension was defined by a systolic BP ≥ 140 mm Hg, a diastolic BP ≥ 90 mm Hg, or use of hypertensive medication together with past diagnosis of hypertension. Laboratory investigations at baseline included plasma homocysteine and fibrinogen.

MRI

All of the imaging studies were done on the same 1.5-T system with a standard birdcage headcoil. The following sequences were obtained at both time points: T1-weighted axial, coronal, and sagittal scouts, which were used to prescribe a precise imaging plane; a dual-echo (DE) turbo spin-echo (24 axial slices, thickness 5 mm, no gap, repetition time = 3300 ms, echo time = 16/98 ms; field of view = 188 × 250, and Matrix 192 × 256); a T1-weighted spin-echo (repetition time = 768 ms, echo time = 14 ms; rectangular field of view = 188 × 250, and Matrix = 192 × 256); and a pulsed-gradient spin-echo single shot echo-planar pulse sequence (interecho spacing = 0.8 and echo time = 123 ms), with diffusion gradients applied in 8 noncollinear directions chosen to cover 3D space uniformly (duration, 25 ms; maximum amplitude, 21 mT/m; and 2 b-values, 0 and 1044 s/mm²).

Fat saturation was performed using a train of 4 binomial radiofrequency pulses. Axial DE slices and T1-weighted slices were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum. Diffusion-weighted images (10 axial slices, 5-mm section thickness, 128 × 128 matrix, and field of vision 240 × 240) were acquired with the same orientation as the DE images with the middle slices matched onto the middle slices of the DE images. This brain portion was chosen because it is a common location for the CADASIL lesion and is related to the anterior cerebral circulation. For follow-up scans, the anatomical planes were repositioned according to published guidelines.

Image Analysis and Postprocessing

For lesion volumetry we applied a previously established and validated 2-step procedure on all of the baseline and follow-up images. First, regions of abnormal hyperintense signal were identified and marked by 2 experienced readers on hardcopies of T2 and proton density (PD) images. Next, a local threshold based segmentation technique was applied on the lesions on the digital PD-weighted images by trained radiological technicians using the marked PD lesions as a working template. This provided an absolute total lesion volume for all of the baseline and follow-up scans.

Lesion volumes were calculated for both the full set of 24 slices (whole brain) and the 10 central slices corresponding to the diffusion-weighted images. The diffusion tensor was estimated from the diffusion images, and maps of MD were produced as published elsewhere. MD maps were cleaned from extracerebral tissue using a semiautomated threshold procedure followed by manual refinement where necessary. The inner table of the skull was defined as a peripheral cerebrospinal fluid (CSF) space were included. A cutoff threshold of MD > 1.9 × 10⁻³ mm²/s was applied using SPM99 software to suppress the influence of macroscopical CSF. Repeated image review had shown that no false exclusion of nonlacunar lesions occurred at this conservative threshold. Histograms with 4000 bins (width, 0.001 × 10⁻³ mm²/s) were produced from all of the remaining voxels. To allow interindividual histogram comparison, bin counts were normalized by division through the total number of all voxels different from zero.

Statistical Methods

Statistical inferences regarding changes of clinical scores and MRI measures were based on Wilcoxon tests for dependent samples. Correlations between clinical and MRI measures were calculated using the Spearman rank correlation coefficient (SRCC) and the partial correlation coefficient where appropriate. Bivariate exploration of determinants of clinical deterioration and changes of average MD were based on the SRCC and the corresponding tests. Independent variables were selected on the basis of epidemiological data suggesting a role for age, systolic blood pressure, and homocysteine levels in SVD. We additionally included the time between baseline and follow-up, gender, T2-leSION volume (whole brain), and average MD at baseline based on previous data suggesting a possible role of these factors in determining disease progression in CADASIL.

Multivariate analysis of outcomes was done using linear regression (average MD, Rankin, and SIDAM) or logistic regression (stroke occurrence) with forward selection. Regressors with a P < 0.05 were included in the respective models. Statistical analyses were done with SPSS version 12.0.1 for Windows (SPSS Inc.). Sample sizes were calculated as described previously.

Results

Sixty-two CADASIL subjects (27 men and 35 women, aged 44.4 ± 9.6 years) completed the protocol and were thus included into the analysis. All but 2 of them had developed symptoms. The mean interval between baseline and follow-up was 26.3 ± 1.2 months (range, 23.6 to 30.9 months).

Clinical and Neuroimaging Characteristics

The mean clinical scores and MRI characteristics obtained at baseline and at follow-up are shown in Table 1. At follow-up, all of the clinical scales had deteriorated when compared with baseline. Twelve individuals had developed new strokes. The volume of T2/PD-weighted lesions had significantly increased (Table 1; Figure 1A). Also, average values and peak locations of MD histograms had significantly increased, and peak heights had significantly decreased (Table 1; Figure 1B). In controls, no significant changes of any MRI characteristics were found.
To assess how consistently imaging and clinical measures deteriorated over time, we computed the proportion of CADASIL subjects in whom the measures in Table 1 worsened. Worsening was defined as a deterioration of clinical scales, an increase in T2-lesion volumes, an increase in average values and peak locations of MD histograms, and a decrease in peak heights of MD histograms. As shown in Table 1, the proportion of worseners was generally higher with imaging than with clinical measures.

**Correlations Between Neuroimaging Characteristics and Clinical Scales**

The volume of T2-visible lesions, average MD, and peak heights of MD histograms significantly correlated with clinical scores (Table 2). In contrast, peak locations showed no significant correlation with clinical scores.

To identify factors that would predict progression of MRI characteristics and clinical scores on a longitudinal scale (Table 3). Changes of average MD correlated with changes of the Rankin score (Figure 2A), National Institutes of Health Stroke Scale score, and SIDAM score (Figure 2B; all $P<0.01$) with a nonsignificant trend for the Barthel ($P=0.07$) and Mattis dementia rating scale score ($P=0.11$). In contrast, there was no significant correlation between changes of T2-lesion volume and changes of any of the clinical scales.

**Prognostic Factors**

To identify factors that would predict progression of MRI measures, we looked at changes of either T2-lesion volume or average MD as the dependent variable and the following independent baseline variables: age, gender, systolic blood pressure, homocysteine level, T2-lesion volume, and average MD.

In bivariate correlations, average MD (SRCC=0.51; $P<0.001$), age (SRCC=0.50; $P<0.001$), T2-lesion volume (SRCC=0.37; $P=0.003$), and systolic blood pressure (SRCC=0.35; $P=0.006$) were found to predict changes in average MD during follow-up. In contrast, there was no significant correlation between any of the independent variables and changes of T2-lesion volume during follow-up. On multivariate analysis, the average MD at baseline ($P<0.001$) and systolic blood pressure at baseline ($P=0.006$) were the only predictors of changes in average MD during follow-up explaining about one-third of the variance ($R^2=0.34$).

To identify factors that would predict clinical worsening, we looked at the following dependent variables: changes of the Rankin score, changes of the SIDAM score, and newly occurring strokes. On multivariate analysis, the average MD at baseline was the only significant predictor for changes of the Rankin score (0.04 points per $0.01\times10^{-3}$ mm$^2$/s of average MD; $P=0.002$), changes of the SIDAM score (0.28 points per $0.01\times10^{-3}$ mm$^2$/s of average MD; $P=0.012$), and newly occurring strokes (odds ratio, 1.34 per $0.01\times10^{-3}$ mm$^2$/s of average MD; $P=0.001$).

**Sample Size Estimates**

To explore the possible role of MRI for future interventional trials, we performed sample size calculations using longitudinal data from the current study. Table 4 indicates the number of subjects needed for inclusion assuming a trial duration of 2 years, a power of 80%, and a type I error probability of 0.05.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Measures and Magnetic Resonance Measures at Baseline and at Follow-up</th>
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</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Cases (n=62)</strong></td>
</tr>
<tr>
<td><strong>Clinical scales</strong></td>
</tr>
<tr>
<td>Rankin score</td>
</tr>
<tr>
<td>Barthel Index</td>
</tr>
<tr>
<td>NIHSS score</td>
</tr>
<tr>
<td>SIDAM score</td>
</tr>
<tr>
<td>MDRS score</td>
</tr>
<tr>
<td>T2-lesion volumes (whole brain; ccm$^3$)</td>
</tr>
<tr>
<td>T2-lesion volumes (central slices; ccm$^3$)</td>
</tr>
<tr>
<td><strong>Mean diffusivity histograms</strong></td>
</tr>
<tr>
<td>Average value ($\times10^{-3}$ mm$^2$/s)</td>
</tr>
<tr>
<td>Peak height (%)</td>
</tr>
<tr>
<td>Peak location ($\times10^{-3}$ mm$^2$/s)</td>
</tr>
<tr>
<td><strong>Controls (n=7)</strong></td>
</tr>
<tr>
<td>T2-lesion volumes (ccm$^3$)</td>
</tr>
<tr>
<td><strong>Mean diffusivity histograms</strong></td>
</tr>
<tr>
<td>Average value ($\times10^{-3}$ mm$^2$/s)</td>
</tr>
<tr>
<td>Peak height (%)</td>
</tr>
<tr>
<td>Peak location ($\times10^{-3}$ mm$^2$/s)</td>
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</tbody>
</table>

Mean interval between baseline and follow-up: 26.3±1.2 months (CADASIL) and 24.15±2.7 months (controls).
Discussion

The current prospective study, which was conducted in a large cohort of CADASIL subjects, establishes significant correlations between magnetic resonance diffusion histogram metrics and clinical measures on a longitudinal scale. Sample size estimates showed that the number of patients needed to demonstrate a treatment effect in an interventional trial is lower with neuroimaging than with clinical end points. Moreover, our data suggest a role for MD histograms in predicting disease progression.

The results obtained at baseline extend previous studies by demonstrating that both the volume of T2-visible lesion and average values of MD histograms correlate with multiple clinical measures including disability, activities of daily living, neurological outcome, and cognition.

Whereas the volume of T2-lesions was correlated with clinical scales at baseline, there was no correlation on a longitudinal scale, that is, between changes of T2-lesion volumes and changes of clinical scales. One explanation for a failure to observe such a correlation, aside from noise in the data itself, rests with possible interference of brain atrophy. Conceivably, brain atrophy, which was not investigated in the current study, might counteract lesion growth, and, in fact, there were several individuals in which a decrease of T2-lesion volumes between baseline and follow-up was observed (data not shown).

![Figure 1. (A) example of the progression of T2-visible lesions in a 39-year-old female CADASIL patient (2-year interval); (B) MD histograms in CADASIL subjects (n=62) and controls (n=7) at baseline and at follow-up.](image)

![Table 2. Correlations Between Neuroimaging Measures and Clinical Scales at Baseline in 62 CADASIL Subjects](table)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rankin Score, r</th>
<th>Barthel Index, r</th>
<th>NIHSS Score, r</th>
<th>SIDAM Score, r</th>
<th>MDRS Score, r</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-lesion volumes, whole brain (ccm³)</td>
<td>0.50†</td>
<td>-0.36†</td>
<td>0.45</td>
<td>-0.26*</td>
<td>-0.19</td>
</tr>
<tr>
<td>T2-lesion volumes, central slices (ccm³)</td>
<td>0.54†</td>
<td>-0.38†</td>
<td>0.47†</td>
<td>-0.34†</td>
<td>-0.27*</td>
</tr>
<tr>
<td>Mean diffusivity histograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average value, $\times 10^{-3}$ mm²/s</td>
<td>0.60†</td>
<td>-0.42†</td>
<td>0.49†</td>
<td>-0.43†</td>
<td>-0.45†</td>
</tr>
<tr>
<td>Peak height, %</td>
<td>-0.62†</td>
<td>0.38†</td>
<td>-0.54†</td>
<td>0.47†</td>
<td>0.46†</td>
</tr>
<tr>
<td>Peak location, $\times 10^{-3}$ mm²/s</td>
<td>0.23</td>
<td>-0.14</td>
<td>0.16</td>
<td>-0.16</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

r indicates Spearman rank correlation coefficient. *P<0.05; †P<0.01; ‡P<0.001.
alternative explanation would be a ceiling effect in patients who have extensive white matter lesions. Finally, the volume of T2-visible lesions may be clinically less important than the severity of tissue damage within T2-lesions and within brain tissue appearing normal on T2 images.

DTI provides quantitative information on the degree of tissue damage within areas that are hyperintense on T2 images, and the MD within such lesions was shown to correlate with clinical measures in earlier cross-sectional studies.\textsuperscript{21–23} Moreover, DTI is sensitive in detecting tissue changes within brain tissue appearing normal on conventional MRIs, and, again, such changes were found to be clinically relevant.\textsuperscript{10,21,23} Thus, compared with lesion volumes, MD histograms might be expected to provide a more comprehensive view of the extent of tissue damage within the brain.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔRankin Score, $r$</th>
<th>ΔBarthel Index, $r$</th>
<th>ΔNIHSS Score, $r$</th>
<th>ΔSIDAM Score, $r$</th>
<th>ΔMDRS Score, $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔT2-lesion volumes, whole brain (ccm³)</td>
<td>0.07</td>
<td>-0.13</td>
<td>-0.05</td>
<td>-0.14</td>
<td>-0.01</td>
</tr>
<tr>
<td>ΔT2-lesion volumes, central slices (ccm³)</td>
<td>-0.01</td>
<td>-0.16</td>
<td>-0.06</td>
<td>-0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean diffusivity histograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔAverage value, $\times 10^{-3}$ mm²/s</td>
<td>0.36$^†$</td>
<td>-0.23</td>
<td>0.36$^†$</td>
<td>-0.47$‡$</td>
<td>-0.21</td>
</tr>
<tr>
<td>ΔPeak height, %</td>
<td>-0.01</td>
<td>0.05</td>
<td>-0.09</td>
<td>0.25$^*$</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔPeak location, $\times 10^{-3}$ mm²/s</td>
<td>0.24</td>
<td>-0.14</td>
<td>0.35$^†$</td>
<td>-0.33$†$</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

For legend see Table 2; Δ indicates change between baseline and follow-up.

**Figure 2.** Scatterplots of the change of average MD versus the change of clinical status during follow-up in the 62 CADASIL subjects: (A) disability scores (Rankin); (B) cognitive scores (SIDAM).
In support of this, we found significant correlations between changes of average MD and changes of clinical scales over time. Again, correlations were found for multiple clinical aspects, including disability, neurological outcome, and cognition. These findings emphasize the importance of MD histogram metrics and show that increases in MD reflect a clinically important aspect of the pathology. Of note, the measures in Table 1 all changed in the expected direction over time. However, decline was much more consistently seen with imaging than with clinical measures, suggesting that MRI is superior in detecting changes over time.

Our findings have important implications. Because of their sensitivity in detecting changes and the observed correlations with clinical scales, diffusion histograms seem suited as an adjunct outcome measure in future interventional trials. Additional criteria must be met to establish MRI as an adjunct outcome measure in future interventional trials. Importantly, however, varying the threshold between threshold, most of the signal from lacunar infarcts and sulcal supression of macroscopic CSF from the MD maps. Using this finding that is also supported by the lack of changes in our control individuals; (2) the area of interest covered a large and representative portion of the brain, which is the major site of pathology in CADASIL; and (3) any inaccuracy attributable to incomplete coverage would likely jeopardize rather than enhance the observed correlations with clinical scales. Another possible limitation is the use of relatively crude measures of cognitive functioning instead of dedicated neuropsychological test batteries, such as the Vascular-Alzheimer Disease Assessment Scale-Cognitive Subscale. Thus, the relationship with specific aspects of cognition, such as executive function, remain unexplored. Additional studies are required to address these and other issues, such as the role of brain atrophy and the volume of T1-lesions.

In the current study, we used a fixed threshold for suppression of macroscopic CSF from the MD maps. Using this threshold, most of the signal from lacunar infarcts and sulcal CSF was removed. Thresholding additionally influences the impact of partial volume effects and, thus, brain atrophy on average MD. These issues need to be considered in future studies. Importantly, however, varying the threshold between 1.7×10⁻³ mm²/s and 1.9×10⁻³ mm²/s had no significant effect on longitudinal changes of MD (data not shown).

To our knowledge, this is the first study to formally address correlations between longitudinal changes of quantitative MRI metrics and changes of clinical scales in patients with subcortical ischemic lesions. Our findings cannot be generalized to the large group of patients with sporadic SVD. Yet, there are many similarities between CADASIL and sporadic SVD. We, therefore, speculate that DTI histograms might follow-up, but it might be that CADASIL follows an accelerated course.

We also identified systolic blood pressure as a risk factor for increases in MD during follow-up. This finding agrees with epidemiological data showing that systolic blood pressure is a main risk factor for cerebral white matter lesions. It additionally demonstrates that the phenotype in CADASIL may be modified by conventional risk factors. Finally, and most importantly, our data suggest that CADASIL subjects might benefit from antihypertensive treatment, although the optimal blood pressure levels in these patients are still unknown. Additional studies are needed to resolve this issue. Hypertensive patients who have high values of average MD on brain MRI are at an elevated risk for clinical progression and may, thus, need closer follow-up with rigid blood pressure control.

Of note, the volume of T2-visible lesions at baseline was not a predictor of progression during follow-up. This finding contrasts population-based studies that found progression of T2-lesions mainly in individuals with higher baseline grades of white matter hyperintensities. However, these studies are difficult to compare because of different methods in lesion quantification and statistical analysis.

Our study also has possible limitations, which need to be considered. Brain coverage for the DTI measurements was incomplete. However, we consider it unlikely that this limitation affects our main findings, for the following reasons: (1) imaging-reimaging studies with a similar protocol have shown that the reproducibility of this method is high, a finding that is also supported by the lack of changes in our control individuals; (2) the area of interest covered a large and representative portion of the brain, which is the major site of pathology in CADASIL; and (3) any inaccuracy attributable to incomplete coverage would likely jeopardize rather than enhance the observed correlations with clinical scales. Another possible limitation is the use of relatively crude measures of cognitive functioning instead of dedicated neuropsychological test batteries, such as the Vascular-Alzheimer Disease Assessment Scale-Cognitive Subscale. Thus, the relationship with specific aspects of cognition, such as executive function, remain unexplored. Additional studies are required to address these and other issues, such as the role of brain atrophy and the volume of T1-lesions.

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also be suited to monitor the progression of white matter lesions secondary to sporadic SVD.

Acknowledgments
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References
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