Brain Atrophy Is Related to Lacunar Lesions and Tissue Microstructural Changes in CADASIL

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Background and Purpose—Cerebral atrophy has been recently recognized as a key marker of disease progression in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The contribution of subcortical cerebral lesions in this process remains undetermined. The aim of this study was to investigate the relationships between cerebral volume and different types of subcortical MRI lesions in CADASIL.

Methods—Demographic, clinical, and laboratory data from 147 patients with CADASIL recruited from a prospective cohort study were analyzed. Validated methods were used to determine the ratio of brain volume to intracranial cavity volume (brain parenchymal fraction [BPF]), volume of white matter hyperintensities, volume of lacunar lesions, number of cerebral microhemorrhages, and mean apparent diffusion coefficient. Associations between BPF, clinical scales, and the different subcortical MRI markers were tested.

Results—BPF obtained in 129 patients was significantly associated with the Mattis dementia rating scale (P<0.0001), Mini-Mental State Examination (P=0.002), and modified Rankin scale (P<0.0001) after adjustment for age and sex. Multiple linear regression modeling showed that BPF was independently associated with mean apparent diffusion coefficient (P<0.0001), volume of lacunar lesions (P=0.004), and age (P<0.0001), accounting for 46% of the observed variance in BPF but not with volume of white matter hyperintensities or number of microhemorrhages.

Conclusions—In association with age, mean apparent diffusion coefficient and volume of lacunar lesions are strong and independent MRI predictors of BPF, a key marker of cognitive and motor disability in CADASIL. These results suggest brain atrophy is related to remote and/or diffuse consequences of both lacunar lesions and widespread microstructural alterations within the brain outside lacunar lesions. (Stroke. 2007;38:1786-1790.)

Key Words: CADASIL ■ cerebral atrophy ■ cerebral microhemorrhage ■ diffusion ■ lacune ■ white matter hyperintensities

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic cerebral microangiopathy leading to disability and dementia.1 It is caused by mutations in the Notch3 gene on chromosome 192 and is considered a genetic model of “pure” subcortical ischemic vascular dementia.

Three types of lesions are seen on conventional MRI sequences. White matter hyperintensities (WMH) are detected on T2-weighted or fluid attenuated inversion recovery images. They are commonly symmetrical, diffuse, and confluent3 and often involve the temporal poles.4 Lacunar lesions (LL) are hypointense on T1-weighted images5 and appear of various shapes and sizes6 as reported pathologically.7 Cerebral microhemorrhages (CM) appear as rounded hypointense foci on T2* or gradient echo images and are detected in approximately one third of patients.8 Additionally, microstructural changes detected by diffusion imaging both inside WMH and in normal-appearing white matter have been previously reported to be strongly associated with motor and cognitive decline.9,10

Recently, normalized brain volume was found to be strongly correlated with cognitive and disability scales in cerebral microangiopathies.11,12 These results, also reported in CADASIL, both in cross-sectional and longitudinal analyses,13 suggest that brain atrophy may represent a “final common pathway” in the pathophysiology of microangiopa-
ties. Peters et al recently observed an atrophy rate 3 times higher in 76 patients with CADASIL compared with rates in normal aging independent from the extent of WMH. However, they did not investigate the potential impact of LL, CM, or microstructural changes (assessed by diffusion imaging) on this process.13

The aim of the present study was to investigate the relationships between different MRI markers of subcortical tissue lesions as assessed with routine MRI sequences (including apparent diffusion coefficient [ADC] measured with diffusion-weighted imaging) and brain volume in a large series of patients with CADASIL.

Materials and Methods

Subjects

One hundred forty-seven subjects (107 from Paris and 40 from Munich) were recruited among consecutive CADASIL patients with a positive genetic test and at least 18 years of age evaluated at Lariboisière (Paris) or Ludwig-Maximilians-Universität (Munich) hospitals between October 2003 and July 2005. Complete study design has been detailed elsewhere.8 Clinical and demographic data were collected, including age, sex, history of hypertension (defined as diagnosis of hypertension or taking antihypertensive drugs), systolic blood pressure, diastolic blood pressure, diabetes (1997 World Health Organization criteria), history of hypercholesterolemia (diagnosis of hypercholesterolemia or taking lipid-lowering drugs), smoking habits, alcohol intake, and body mass index. Laboratory evaluation (which included complete blood count, glucose, hemoglobin A1c, homocysteine, high-density lipoprotein, low-density lipoprotein, and total cholesterol levels) was performed in all patients. All subjects underwent detailed baseline neurological examination during the 2 hours before MRI examination, including a Mini-Mental State Examination, Mattis dementia rating scale, and degree of disability based on the modified Rankin scale and Barthel index. An independent ethics committee in both participating centers approved this study.

MRI

MRI scans were obtained by the use of a 1.5-T system (Vision; Siemens [Munich] or Signa General Electric Medical Systems [Paris]). Three dimensional T1-weighted axial sequences (Munich: TR/TE 11/4.4 ms, slice thickness 1.19 mm, no interslice gap, 256×256; Paris: TR/TE 9/2 ms, slice thickness 0.8 mm, no interslice gap, 256×256), fluid-attenuated inversion recovery (FLAIR; Munich: TR/TE/TR/TE 1452/484/110/1428, slice thickness 5 mm, no interslice gap, 176×256; Paris: TR/TE/TE 500/15/15002 ms, slice thickness 5.5 mm, no interslice gap, 256×160), T2*-weighted gradient echo planar imaging (Munich: TR/TE 1056/22 ms, slice thickness 5 mm, no interslice gap, 256×192; Paris: TR/TE 500/15 ms, slice thickness 5.5 mm, no interslice gap, 256×192), proton density (Munich: TR/TE/TE 192/3300/16 ms, slice thickness 5 mm, no interslice gap, 190×256; Paris: TR/TE 3300/15 ms, slice thickness 5.5 mm, no interslice gap, 256×192), and diffusion-weighted imaging (Munich: TR/TE/TI 5100/137 ms, slice thickness 5 mm, interslice gap 1.5 mm, 128×128; Paris: TR/TE 8200/83 ms, slice thickness 5.5 mm, interslice gap 1.5 mm, 128×128; b value = 1000 s/mm²) were performed. Diffusion-weighted imaging scans were acquired in the X, Y, and Z directions and then averaged to make ADC measurements largely independent of the effects of anisotropic diffusion. Apparent diffusion coefficient values were then calculated to generate ADC maps as described elsewhere.14

Image Processing and Analysis

Brain Volume Assessment

Determination of global brain volumes from 3-dimensional T1 sequences was performed using Brainvisa software (CEA, Orsay, France, http://brainvisa.info). The first step consisted of a field inhomogeneity bias correction with an algorithm detailed previously.14 Extraction of nonbrain tissue and segmentation of images into gray matter, white matter, and cerebrospinal fluid (CSF) were done using a validated histogram analysis algorithm.16 Because of large amounts of signal abnormalities in white matter, which can result in voxel misclassification, a manual correction was performed after visual examination of the initial results based on the variance of intensity in gray matter voxels. This correction was performed to obtain the minimal and best matching of the external cerebral contours by visual inspection. To assess validity and reliability of this method, two raters (E.J. and A.V.) performed the task in a double-blind manner on a randomly chosen subset of 20 scans. Intrarater and interrater correlations coefficients were found to be excellent: 0.945 and 0.922. During the segmentation process, all voxels containing CSF (including lacunar cavities) were excluded from the brain volume. Segmentation was performed from the vertex of the brain to the lowest axial slice, including cerebellar tissue. Automated determination of the volume of the intracranial cavity was done on proton density images from base to top of the skull using a dedicated algorithm from Therayls (Lyon, France). The corresponding mask was visually checked and marginally corrected if necessary. Brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume to total intracranial cavity volume: BPF = brain tissue volume/intracranial cavity.

Determination of Mean Apparent Diffusion Coefficient

Histograms of ADC values from ADC maps were generated for each patient using a bin width equal to 0.1 10⁻⁴ mm²/s. Voxels containing CSF were excluded in all patients before calculation using a superior threshold value at 27 10⁻⁴ mm²/s (after careful visual analysis of masks generated with different threshold values). To correct for cross-subject differences in brain volume, each histogram was normalized to the total number of brain tissue voxels. Only the mean ADC derived from each histogram was used for analysis.

Lesions Quantification

Lesion quantification was made as previously described.8 Briefly, WMH were analyzed on all axial FLAIR slices from the base of the cerebellum to the vertex. LL were determined on 3-dimensional T1 scans. The total volume of WMH and LL were normalized to the intracranial cavity in each patient [normalized volume = (volume/intracranial cavity) × 100]. The number of CM, defined as rounded foci 5 mm or less in diameter hypointense on gradient echo sequences and distinct from vascular flow voids, leptomeningeal hemosiderosis, or nonhemorrhagic subcortical mineralization, was recorded.

Statistical Methods

Correlations between clinical and MRI measures were calculated using the Spearman’s rank correlation coefficient and partial correlation coefficient when needed. Linear regressions were performed using Pearson’s product moment correlation to assess the relative contribution of clinical and MRI variables on BPF. Variables were selected on the basis of published epidemiological data: age, gender, systolic and diastolic blood pressure, homocysteine levels, cholesterol levels, body mass index, fasting glucose, hemoglobin A1c, and diabetes. Traditional cardiovascular risk factors such as smoking habits and alcohol intake were also included. Both conventional MRI markers and mean ADC values were analyzed in the models. A log transformation was performed for normalized volume of WMH and LL to obtain normal distributions, thus defining vWMH and vLL, respectively. For analysis, number of CM values was divided into tertiles (0, 1 to 3, or 4 or more).

Multivariable linear regression models were used to find predictors of BPF. Candidate covariates were those associated with BPF in univariate analysis (P < 0.10). Center effect was analyzed using a fixed-effects model. The final model variables were selected by a stepwise regression analysis with entry and removal values set to 0.05.
Demographic, Imaging, and Cognitive Features in 129 Patients With CADASIL

Clinical variables

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD (range)</td>
<td>51.37±11.39 (26–78)</td>
</tr>
<tr>
<td>Male sex</td>
<td>56/129 (43%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>20/128 (16%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.59±4.35</td>
</tr>
<tr>
<td>Current or previous smoking</td>
<td>62/129 (48%)</td>
</tr>
<tr>
<td>Any alcohol consumption</td>
<td>70/119 (59%)</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>64/128 (50%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3/128 (2.3%)</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agent use</td>
<td>90/129 (70%)</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>5/129 (3.9%)</td>
</tr>
</tbody>
</table>

Disability and cognitive scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel index, mean, median (range)</td>
<td>89.2, 100 (0–100)</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale, mean, median (range)</td>
<td>1.9, 0 (0–25)</td>
</tr>
<tr>
<td>Rankin’s scale, mean, median (range)</td>
<td>1.1, 0 (0–5)</td>
</tr>
<tr>
<td>Mini-Mental State Examination, mean, median (range)</td>
<td>26.1, 28 (7–30)</td>
</tr>
<tr>
<td>Mattis dementia rating scale, mean, median (range)</td>
<td>131.8, 141 (35–144)</td>
</tr>
</tbody>
</table>

MRI markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPF, mean±SD</td>
<td>80.7±6.2</td>
</tr>
<tr>
<td>Absolute volume of LL, mm³, median (range)</td>
<td>524.3 (0–5708.07)</td>
</tr>
<tr>
<td>Normalized volume of LL, median (range)</td>
<td>0.04 (0–0.41)</td>
</tr>
<tr>
<td>Absolute volume of WMH, mm³, median (range)</td>
<td>88921 (3819–334,289)</td>
</tr>
<tr>
<td>Normalized volume of WMH, median (range)</td>
<td>6.25 (0.27–22.69)</td>
</tr>
<tr>
<td>No. of CM,* median (range)</td>
<td>4 (0–26)</td>
</tr>
<tr>
<td>Mean ADC (10⁻¹⁴ mm² s⁻¹), mean±SD</td>
<td>12.11±1.59</td>
</tr>
</tbody>
</table>

*Calculated only in patients with CM.

Results

Among the 147 patients from the cohort, 129 patients had full sets of 3-dimensional T1, FLAIR, proton density, T2*, and diffusion-weighted images of sufficient quality for postprocessing measurements. Their demographic, clinical, and main MRI parameters are presented in Table 1.

After adjustment for age and sex, BPF was found to be significantly correlated with Mattis dementia rating scale (Spearman rank correlation coefficient, ρ=0.43, P<0.0001), Mini-Mental State Examination score (ρ=0.28, P=0.002), Barthel index (ρ=0.42, P<0.0001), modified Rankin score (ρ=−0.41, P<0.0001), and National Institutes of Health Stroke Scale score (ρ=−0.41, P<0.0001).

In univariate linear regression analyses for demographic and clinical variables, BPF was inversely related to age (Pearson’s correlation coefficient, r=−0.50, P<0.0001) male gender (r=−0.27, P=0.002), and hypercholesterolemia (r=−0.21, P=0.02). Conversely, no correlation was detected between BPF and systolic blood pressure, diastolic blood pressure, history of smoking, body mass index, alcohol intake, diabetes, homocysteine, hemoglobin A1c, or fasting glucose levels.

Univariate analyses for MRI markers revealed that BPF correlated with both mean ADC (r=−0.58, P<0.0001), vLL (r=−0.43, P<0.0001), and number of CM (r=−0.30, P=0.0005) but not with vWMH (r=−0.12, P=0.19).

A stepwise multivariate analysis was performed with significant clinical and MRI variables, including a potential center effect. Three variables remained significantly related to BPF: mean ADC (P<0.0001), vLL (P=0.0037), and age (P<0.0001). In the statistical model, these three factors explained 46% of the variance of BPF.

Discussion

In the present study, we found a strong correlation between BPF and both cognitive and disability scales in a large series of patients with CADASIL independent of age and sex. This is in agreement with data recently obtained by Peters et al in 76 patients with CADASIL using a different method for measurement of brain volume (SIENAX). They are also in line with results observed in elderly populations having white matter hyperintensities and/or lacunar infarctions.

We detected a strong correlation between BPF and two MRI markers of the disease, which was independent from the age effect: the volume of LL and the mean ADC (measured over the whole brain and after exclusion of tissue cavities containing CSF). Although the negative impact of the load of small deep infarcts on cognitive function has been repeatedly demonstrated in various populations, only few studies have examined the relationships between the brain volume and the load of small deep infarcts using MRI. In a small study of 27 patients with cerebral microangiopathy, Preul et al recently observed a significant correlation between the severity of T2 lesions (including LL) and both the cortical thickness and ventricle index. Conversely, in the Atherosclerosis Risk in Communities study, no association between LL and the enlargement of cerebral ventricles or cortical atrophy was detected. However, in this study, the volume of LL was not evaluated and the degree of atrophy was assessed only by visual scale. Additionally, the number of LL might be significantly lower in this population, because individuals with stroke or transient ischemic attack were excluded from the cohort. It is noteworthy that the association between BPF and LL in our study is unlikely to be related to direct tissue loss caused by lacunar lesions because the results remained unchanged when the volume of LL was included in BPF estimation (data not shown). The results suggest that LL lead to brain volume loss through remote and/or diffuse effects on brain morphology. Apoptosis, recently described in cortical neurons in patients with CADASIL, may participate in this process.

The strong association detected between the reduction of BPF and the increase in mean cerebral ADC is another important result of this study. It has been previously shown that the mean diffusivity measured with diffusion tensor imaging was of great value to assess the severity of microstructural tissue damage during the course of cerebral microangiopathies. The increase in diffusion in CADASIL as...
well as in other cerebral microangiopathies was also found strongly correlated with clinical severity. This increase in diffusion (measured by mean diffusivity or ADC) is presumably related to the enlargement of the extracellular space caused by demyelination and axonal loss. In the current study, diffusion was measured over the whole brain after masking LL. Thus, mean diffusivity was measured in noninfarcted tissue areas both inside and outside regions of WMH. These results in addition to the lack of correlation between brain atrophy and the extent of WMH (as recently reported in a prospective study) strongly suggest that the severity of microstructural tissue damage has a much more potent impact than the extent of WMH on brain atrophy in patients with CADASIL. Of note, in the present study, we did not use diffusion tensor imaging techniques to assess the microstructural tissue status but generated ADC maps from routine diffusion-weighted images. The highly significant results obtained using such a simple parameter suggest that this measure may provide considerable prognostic and therapeutic information in the evaluation of cerebral microangiopathies. The comparison of these different diffusion MRI techniques would be important for future studies.

The lack of association between BPF and the extent of WMH in the present study is in contrast with data obtained in the elderly showing that the extent of WMH is associated with gray matter reduction and may even predict cerebral atrophy. This discrepancy may be related to differences of age, clinical presentation, MRI methods, and quantification techniques in these studies. Also, the load of LL, CM, and the severity of microstructural changes were not taken into account in the previous studies. Altogether, the present data further emphasize that although the extent of WMH (and location) is of great diagnostic value at the initial phase of CADASIL, its actual consequences on cerebral volume as well as on clinical severity may be relatively limited when other types of associated lesions are considered (Figure).

A significant association was detected between BPF and the number of CM that did not remain significant in multivariate analysis. Although we cannot exclude a small effect of CM on the cerebral volume, the inverse correlation with BPF in univariate analysis may also reflect that these lesions are mainly observed at the late stage of the disease when patients have more extensive structural changes in the cerebral tissue. There are potential limitations in the interpretation of our results. First, we were unable to use our brain volume segmentation algorithm in 18 patients attributable to insufficient image quality. Although this could introduce a potential bias in our results, careful visual analysis of the data showed that movement artifacts were mostly responsible for exclusion of these subjects from analysis. Additionally, because our study was cross-sectional, we could not determine whether the increase in the volume of LL or in cerebral diffusion actually precedes the occurrence of cerebral atrophy. Prospective studies may help to understand the link between the structural tissue changes observed at the subcortical level and the reduction of the whole brain volume.

In summary, our results provide convincing evidence that brain atrophy is strongly related to remote or diffuse consequences of both LL and cerebral tissue microstructural damage. In association with age, volume of LL and mean ADC may account for nearly half of the reduction of brain volume in this disorder. Future prospective and pathological studies may help to further elucidate the link between subcortical structural changes and global cerebral atrophy in CADASIL as well as in other cerebral microangiopathies.

Acknowledgments

We acknowledge E. Vicaut and C. Boutron for their help and support in the building of the clinical and MRI database, and M. Boukobza and D. Reizine who participated in the MRI examination of patients.
Sources of Funding
This work was supported by PHRC grant AOR 02-001 (DRC/APHP) and performed with the help of ARNEVA (Association de Recherche en Neurologie Vascular), Hôpital Lariboisière, France, the Deutsche Forschungsgemeinschaft (SFB596/TPA4), and a grant from EISAI Medical Res. Inc (Germany). E.J. was supported by a grant from the European Neurological Society and the Peel Medical Research Trust.

Disclosures
None.

References
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*Stroke*. 2007;38:1786-1790; originally published online April 19, 2007; doi: 10.1161/STROKEAHA.106.478263

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

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