Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic cerebral small vessel disease caused by mutations of the NOTCH3 gene. Recently, in a mouse model of CADASIL, intramyelinic edema was detected in the white matter (WM), which may represent the initial lesions of the disease. We hypothesized that if this mechanism holds true in patients, it would translate in larger WM volume. We aimed to measure WM volume in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy in comparison with age- and sex-matched controls, along with the ratio of cortical surface area to the volume of brain hemispheres as an indirect measure that should be reduced in patients.

Methods—Twenty patients at the early stage of the disease (Mini Mental State Examination >24 and modified Rankin scale ≤1) and 27 age- and sex-matched controls had high-quality 3-Tesla 3DT1 MRI acquisitions. Volumes of brain hemispheres and of WM were determined. The ratio of cortical surface area to the volume of brain hemispheres was evaluated as a proxy of underlying WM volume.

Results—Patients had larger volumes of WM than controls (patients: 479.4±71.7; controls: 463.9±44.2; P=0.03). They presented a lower cortical surface area and cortical volume leading to a lower ratio of cortical surface area to the volume of brain hemispheres (patients: 15.7±0.7; controls: 16.1±0.5; P=0.004). Volume of WM tended to be associated with that of WM hyperintensities (P=0.06).

Conclusions—Patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy have larger WM volume than age- and sex-matched controls, a finding compatible with the hypothesis of intramyelinic edema as observed recently in mice. (Stroke. 2015;46:258-261. DOI: 10.1161/STROKEAHA.114.007018.)

Key Words: CADASIL ■ cerebral small vessel diseases ■ edema ■ white matter diseases
of brain hemispheres should be smaller in patients. Both CSA and the volume of brain hemisphere are reliable measures in the context of small vessel disease as they mostly rely on gray to cerebrospinal fluid contrast, which is unaltered by WM lesions.6

In the present study, we aimed to evaluate whether the volume of WM is larger in patients with CADASIL using both direct and indirect measures at the early clinical stage of the disease.

Methods

Participants

Patients with CADASIL at the early clinical stage of the disease (Mini Mental State Examination score >24 and modified Rankin scale ≤1) were recruited from our French national database on a voluntary basis. Controls were drawn from a local database of healthy volunteers free of any known history of neurological disorder and without symptoms of cognitive impairment or disability as evaluated by a structured interview. Subjects included for this study had high-quality 3DT1 images allowing the study of cortex structure (20 patients and 27 healthy controls). A local ethics committee validated the protocol and all subjects gave their written consent for participating in the study.

Data Acquisition

Three-dimensional T1-weighted images used for volumetric analyses were obtained at 3 Tesla with a Tim-Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 12-channel head coil, using a standard sagittal magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (in plane resolution: coil, using a standard sagittal magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (in plane resolution: 1×1 mm2; slice thickness, 1.1 mm; repetition time, 2300 ms; echo time, 2.98 ms; inversion time, 900 ms; flip angle, 9°; bandwidth, 238 Hz/pixel; and time of acquisition, 7′45 minutes). Lesion masks, volumes of lacunes and of WMH, and number of microhemorrhages were determined from 3DT1, fluid-attenuated inversion-recovery images, and T2* gradient echo images obtained within 6 months on a 1.5T Signa scanner (GE Healthcare, Milwaukee, WI).5,7

Data Processing and Statistical Analysis

Three-dimensional T1-weighted images were processed using FreeSurfer.4 Volumes of WMH (WMHV) were calculated by multiplying the number of voxels corresponding to WMH masks by the voxel size.7 Masks of WMH were registered to 3DT1 images and, as previously reported,7 voxel intensity inside WMH was set up to an average intensity close to that of normal-appearing WM to overcome segmentation difficulties possibly induced by WMH in patients. Reconstructed data sets were systematically inspected for accuracy. Temporal poles as defined in the Desikan–Killiany atlas were excluded from the CSA and cortical thickness measurements because of the frequent signal abnormalities in these regions that may affect the accurate detection of the gray-WM boundary. The volume of brain hemispheres (BHv), volume of hemispheric WM including hypointensities (WMv), average cortical thickness, and CSA were computed for each subject. Ratio of CSA to the BHv was defined as Rsv=CSA/BHv to respect dimensionality.

Statistical analyses were made using the R software (http://www.r-project.org/). Between-group comparisons were performed using χ2 or t tests depending on variable type and distribution. Linear regression modeling was used to test whether volumetric or surface measures differ between groups, with adjustment for potential confounder (age, sex, BHv, and intracranial cavity volume) when necessary.

Table. Characteristics of Patients With CADASIL and Healthy Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CADASIL Patients (n=20)</th>
<th>Healthy Controls (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men), %</td>
<td>50</td>
<td>48</td>
<td>0.98</td>
</tr>
<tr>
<td>Age, mean±SD (range)</td>
<td>53.7±11.8 (32.1–74.5)</td>
<td>53.8±11.2 (30.1–71.4)</td>
<td>0.98</td>
</tr>
<tr>
<td>History of strokes, n (%)</td>
<td>15 (75)</td>
<td>0 (0)</td>
<td>…</td>
</tr>
<tr>
<td>Modified Rankin Scale 0, n (%)</td>
<td>17 (85)</td>
<td>27 (100)</td>
<td>0.87</td>
</tr>
<tr>
<td>MMSE, mean±SD (range)</td>
<td>28.7±1.5 (25–30)</td>
<td>28.9±1.2 (26–30)</td>
<td>0.50*</td>
</tr>
<tr>
<td>Intracranial cavity volume, cm3</td>
<td>1414.3±201.6</td>
<td>1356.6±157.0</td>
<td>0.28*</td>
</tr>
<tr>
<td>Volume of brain hemispheres, cm3</td>
<td>1025.9±121.2</td>
<td>1029.5±82.1</td>
<td>0.07†</td>
</tr>
<tr>
<td>Volume of white matter, cm3</td>
<td>479.4±71.7</td>
<td>463.9±44.2</td>
<td>0.03§$</td>
</tr>
<tr>
<td>Cortical surface area, cm2</td>
<td>1600.3±178.6</td>
<td>1641.7±117.9</td>
<td>0.03§$</td>
</tr>
<tr>
<td>Ratio of cortical surface area to the volume of brain hemispheres</td>
<td>15.7±0.7</td>
<td>16.1±0.5</td>
<td>0.004§$</td>
</tr>
<tr>
<td>Mean cortical thickness, mm</td>
<td>2.44±0.11</td>
<td>2.46±0.08</td>
<td>0.36‡$</td>
</tr>
<tr>
<td>White matter hyperintensity volume, mean, median (range), cm3</td>
<td>77.5, 66.6 (7.3–251.5)</td>
<td>No significant lesions</td>
<td>…</td>
</tr>
<tr>
<td>Lacune volume, mean, median (range), cm3 (n=11/20; 55%)</td>
<td>0.49, 0.30 (0.01–1.36)</td>
<td>0</td>
<td>…</td>
</tr>
<tr>
<td>No. of microhemorrhages, mean, median (range; n=7/20; 35%)</td>
<td>2.7 (2.1–6)</td>
<td>0</td>
<td>…</td>
</tr>
</tbody>
</table>

CADASIL indicates cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; and MMSE: Mini Mental State Examination.

Adjusted for sex and age.

†Adjusted for age, sex, and intracranial cavity.

‡Adjusted for age, sex, volume of brain hemispheres, and intracranial cavity.

§P value <0.05.

|| In patients with such lesions (number given in parentheses).
Figure. Increase of white matter volume in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and its consequences on the ratio of cortical surface area to the volume of brain hemispheres. A, Comparison of native 3DT1 scans illustrating our results for 3 patients and controls of increasing age. Volume of brain hemispheres seems larger in patients with smaller ventricles. Ratio of cortical surface area to the volume of brain hemisphere is smaller in patients than in controls. For general understanding, arrows point out some abnormal white matter areas. B, Putative mechanisms to explain the observed differences between controls and patients, described on a schematic of axial MRI slices: (1) classical small vessel disease–related mechanism leading to global brain atrophy; (2) white matter edema leading to an increase of white matter volume; and (3) combination of (1) and (2) explaining smaller ratios of cortical surface areas to the volume of brain hemispheres in patients.
the CSA differences, the $R_w$ was smaller in patients in comparison with controls after adjustment for age, sex, and intracranial cavity volume (estimate=0.46; SE, 0.15; $P$=0.004). In patients, $WM_v$ and $WMH_v$ were marginally associated (estimate=0.32; SE, 0.16; $P$=0.06).

**Discussion**

In the present study, we observed that patients with CADASIL have larger $WM_v$ compared with age- and sex-matched controls at the early stage of clinical manifestations of the disease. We also observed a trend for association between larger $WM_v$ and larger $WMH_v$ among patients (Figure [A]).

The larger $WM_v$ were associated with smaller ratios of CSA to BH$_v$ in patients. Thus, both direct and indirect measures are consistent with the hypothesis of larger $WM_v$ in patients compared with age- and sex-matched controls. In addition to the present findings, we observed that CSA is smaller in patients after adjustment for brain volume, in the absence of significant difference of cortical thickness. These results may be explained by the combination of 2 distinct but concurrent mechanisms: one leading to global brain atrophy with reduction of $WM_v$ cortical volume, and cortical surface, as usually thought in ischemic small vessel disease (Figure [B], mechanism 1); a second mechanism leading to a selective increase of $WM_v$, which would compensate the global brain tissue loss, resulting in a lower ratio of CSA to BH$_v$ without apparent brain atrophy (Figure [B], mechanism 2). The second phenomenon would be explained by intramyelinic edema within the WM. The concomitant occurrence of both mechanisms would thus provide an explanation of the observed difference between patients and controls (Figure [B], mechanism 3). These competing mechanisms may explain why brain atrophy is the most visible feature observed in severe CADASIL patients, particularly in samples including individuals with high loads of lacunar lesions, whereas patients with the most extensive WMH seem to have larger brains than controls. This would also explain some recent unexpected results from the literature. Indeed, in a 7-year follow-up study of patients with CADASIL aged 51.4 years, significant ventricular enlargement was detected in controls but not in patients. Alternatively, we cannot exclude that ratio of CSA to BH$_v$ is lower in patients because of innate group differences possibly related to NOTCH3 mutations. However, this would not explain the larger brain volumes previously observed in patients with the highest extent of WMH.

Our study has some limitations. First, the sample size was small. In addition, the methodology used to measure $WM_v$ may not be completely reliable as WM is frankly abnormal in patients with CADASIL (see Figure). Half of the patients had lacunes in the WM, which may also alter the $WM_v$ estimation. Finally, WM is darker on 3D1 sequences in patients with CADASIL compared with controls, leading to potential errors when estimating the relative volume of gray and WM. However, all these potential sources of error would lead to underestimation of $WM_v$ in patients and are thus unlikely to explain the present results. Moreover, the measures obtained using a proxy of $WM_v$ more reliable, showed results consistent with our initial hypothesis. Given the recruitment criteria of the present study, we could not evaluate whether similar findings can be observed in later stages of CADASIL. However, severe forms of the disease are associated with important brain atrophy and severe signal and contrast alterations that would render this study difficult. Finally, additional investigations are needed to evaluate whether these early alterations are associated with cognitive dysfunction.

**Sources of Funding**

This work was funded by a Network of European Funding for Neuroscience Research grant (01EW1207) under the Seventh Framework Programme and the European Research Area Net, with the support of the French-cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy association, the PLANIOL Foundation, the NRJ Foundation, and the Leducq Foundation.

**Disclosures**

None.

**References**


2. De Guio et al White Matter Edema at the Early Stage of CADASIL.


White Matter Edema at the Early Stage of Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy
François De Guio, Jean-François Mangin, Marco Duering, Stefan Ropele, Hugues Chabriat and Eric Jouvent

Stroke. 2015;46:258-261; originally published online November 4, 2014;
doi: 10.1161/STROKEAHA.114.007018
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/1/258

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/