Correlations Between Clinical Findings and Magnetization Transfer Imaging Metrics of Tissue Damage in Individuals With Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

G. Iannucci, MD; M. Dichgans, MD; M. Rovaris, MD; R. Brüning, MD; T. Gasser, MD; L. Giacomotti; T.A. Yousry, MD; M. Filippi, MD

Background and Purpose—We obtained magnetization transfer imaging (MTI) scans from individuals with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (1) to investigate the presence, extent, and nature of pathology in white and gray matter outside proton density (PD)-visible lesions; (2) to quantify the degree of tissue damage occurring in lesions seen on PD-weighted scans; and (3) to correlate MTI-derived measures of disease burden with age, physical disability, and cognitive performance.

Methods—Dual-echo, T1-weighted, and MTI scans of the brain were obtained from 33 individuals with CADASIL and 12 control subjects. Magnetization transfer ratio (MTR) values from PD-visible lesions, normal-appearing white matter (NAWM), and normal-appearing gray matter (NAGM) were measured. Histograms of MTR from the whole brain and normal-appearing brain tissue were also produced.

Results—All MTR values from NAWM and NAGM regions studied were significantly lower for individuals with CADASIL than for control subjects, with the exception of those obtained from the NAWM of the infratentorial structures and the NAGM of the occipital cortex. The average MTR from PD lesions in individuals with CADASIL was significantly lower than that from all the NAWM regions. Average MTR and peak location from whole-brain and normal-appearing brain tissue histograms were significantly lower for individuals with CADASIL than for control subjects. MTR values from NAWM were strongly correlated with the extent of macroscopic lesions and their average MTR. Apart from NAGM, average MTR from all other tissues studied significantly decreased with increasing age, physical disability, and cognitive impairment.

Conclusions—PD lesions of individuals with CADASIL have variable degrees of tissue damage. Brain tissue outside PD abnormalities is also damaged. This study suggests that the extent and the severity of the brain tissue damage are critical factors in determining clinical status in CADASIL. (Stroke. 2001;32:643-648.)

Key Words: CADASIL ■ magnetic resonance imaging ■ magnetization transfer imaging.
observable magnetization. The degree of signal loss depends on the density and nature of the macromolecules in a given tissue. However, the intensity of a region in an image obtained with magnetization transfer (MT) contrast also reflects, as a minimum, the proton density (PD) in that region and relaxation-based weighting (depending on the image acquisition parameter). For this reason, MT data are usually normalized to calculate an index of MT effect that is relatively independent of the other acquisition parameters. Common practice is to calculate the MT ratio (MTR). Low MTR indicates a reduced capacity of the macromolecules in brain tissue to exchange magnetization with the surrounding water molecules, thus reflecting matrix damage. MT characteristics can be analyzed on a region-of-interest (ROI) basis from maps of MTR, giving information about individual lesions or discrete areas of the normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM). The analysis of MT changes can also be performed on a more global basis by use of MTR histograms. This approach allows evaluation of all the MR image pixels corresponding to brain tissue, thus providing a complete assessment of changes at both macroscopic and microscopic levels.

In the present study, we obtained MTI scans from a relatively large sample of individuals with CADASIL (1) to investigate the presence, extent, and nature of pathology in white and gray matter outside PD-visible lesions; (2) to quantify the degree of tissue damage occurring in lesions seen on PD-weighted scans; and (3) to correlate MTI-derived measures of disease burden with age, physical disability, and cognitive performance of individuals with CADASIL.

Subjects and Methods

Patients

Thirty-three individuals with CADASIL (12 women and 21 men; mean age 50 years, SD 10 years) from 25 families were included in the present study. In all the cases, the diagnosis was confirmed either by a skin or muscle biopsy (7 cases) or by the demonstration of a pathogenic mutation within the Notch3 gene (26 cases). Twenty-nine of the 33 individuals included in the study also had clinical manifestations of CADASIL, including (1) ischemic episodes, (2) cognitive deficits, (3) psychiatric symptoms, (4) migraine with aura, and (5) epileptic seizures, or they had variable combinations of all of the above. Disability was graded in all the individuals with CADASIL by use of the Rankin scale. This is a 5-point rating scale that grades patients on the basis of their overall level of independence with reference to previous performance. Grade 0 corresponds to the absence of symptoms, and grade 5 results from the presence of severe handicap and total dependence. In 29 individuals with CADASIL, cognitive performance was assessed by using the Structured Interview for the Diagnosis of the Alzheimer-Type, Multi-Infarct Dementia and Dementias of Other Etiology (SIDAM). The SIDAM comprises a brief structured clinical interview, a range of cognitive tests, which constitute a short neuropsychological battery, and a section for clinical judgment. The SIDAM score is inversely correlated with the severity of the patients' cognitive impairment. The mean SIDAM score of our group of individuals with CADASIL was 44 (range 14 to 54). The remaining 4 individuals either refused to undergo neuropsychological evaluation or were not considered for it because of the presence of severe pseudobulbar palsy. Twelve healthy volunteers (4 women and 8 men) served as control subjects. Their mean age was 42.0 years (SD 8 years). Although age-matching between controls and individuals with CADASIL was not optimal, a previous study did not show significant MT changes between men and women and for individuals aged 36 to 55 years. Local ethical committee approval and informed consent from all the subjects were obtained before inclusion in the study.

Magnetic Resonance Imaging

Brain MRI scans were obtained from all the subjects by use of a 1.5-Tesla system (Vision, Siemens). The following pulse sequences were acquired: (1) dual-echo turbo spin echo (repetition time [TR] 2300 ms, echo time [TE] 14/85 ms, and echo train length 5), (2) 2D gradient echo (GE) (TR 600, TE 7, and α=20°) with and without a saturation pulse (the saturation pulse was an off-resonance radiofrequency pulse centered 1.5 kHz below the water frequency, with a gaussian envelope and a bandwidth of 25 Hz and e=500°), and (3) T1-weighted spin echo (TR 530, TE 20). For all the scans, 20 contiguous axial slices were acquired with a 5-mm slice thickness and an in-plane spatial resolution of 0.9×0.9 mm. All the scans were positioned according to published guidelines.

Image Review and Quantification

Dual-echo and T1-weighted hard copies from all individuals with CADASIL and control subjects were reviewed in a random order by agreement of 2 experienced observers who were unaware of to whom the scans belonged. Hypointense lesions on PD scans and hypointense lesions on T1-weighted scans were identified and marked on the hard copies, as described previously. Lesion volume measurements were then performed by a single observer, again without knowledge of to whom the scans belonged, with use of a semiautomated segmentation technique based on local thresholding.

From the 2 GE images, with and without the saturation pulse, MTR maps were derived according to a method described previously. After image coregistration, with use of a technique based on mutual information, the lesion outlines on the first echo images of the dual-echo scans were superimposed onto the MTR maps, and average lesion MTI was calculated for each subject, as reported elsewhere. For each MTR map and whenever possible, square ROIs (area 3×3 pixels) were placed bilaterally in areas of NAWM (cerebellar hemispheres, internal capsules, the white matter close to the anterior and posterior parts of the lateral ventricles, and the white matter close to the cortical gray matter of the sylvian fissures). Additional ROIs were also placed centrally in the NAWM of thepons and in areas of the NAGM corresponding to both deep gray matter and cortex regions (head of the caudate nucleus, putamen, thalamus, and frontal, temporal, parietal, and occipital cortex), which were analyzed separately. To be considered part of the NAWM or NAGM, an ROI must not have been adjacent to lesions visible on the same slice and on the slices above and below. ROIs were always placed with care to avoid partial volume effects from cerebrospinal fluid (CSF) and gray matter in the case of NAWM-ROIs and CSF and white matter in the case of NAGM-ROIs. Although GE images may be affected by susceptibility artifacts at the level of the skull base, the quality of our GE images was good, and we did not encounter any problem with image coregistration.

We also derived MTR histograms for the whole brain and normal-appearing brain tissue (NABT) from individuals with CADASIL and control subjects, as described previously. Using the same local thresholding technique that was used for lesion segmentation, a single observer, without knowledge of to whom the scans belonged, removed the skull and other extracranial tissues from the MTR maps. Then, MTR histograms for the whole-brain tissue were created. To obtain NABT-MTR histograms, the lesions segmented on the first echo images of the dual-echo scans were superimposed automatically onto the coregistered MTR map, and the areas corresponding to the segmented lesions were nulled out. For brain and NABT histograms, we excluded from the analysis all the pixels with MTR values <10% to eliminate CSF and points corresponding to noise alone. To correct for the between-patient differences in brain volume, each histogram was normalized by dividing it by the total number of pixels included. By doing this, the area under the histogram is made equal to unity for all subjects; thus, comparisons of the features that characterize the shape of the histogram can be made between subjects. For each MTR histogram, we analyzed the location of the histogram peak with respect to the x-axis (ie, the most
For further details, see the text.

In previous studies, we found very low intraobserver variabilities when we measured all the MRI and MTI quantities mentioned above.

### Statistical Analysis

Differences in MTI parameters between CADASIL individuals and control subjects were assessed by a 2-tailed Student t test for nonpaired data, because MTR values had a normal distribution. Univariate correlations were performed by the Spearman rank correlation coefficient. To reflect the relatively large number of statistical comparisons, a value of $P \leq 0.01$ was considered significant, a value of $P \leq 0.05$ and $>0.01$ was considered a significance trend, and values of $P > 0.05$ were not considered significant. A multivariate analysis with age correction was also performed to assess the influence of PD lesion load, average lesion MTR, NAWM-MTR, cortical NAGM-MTR, and basal nuclei NAGM-MTR on physical disability (Rankin score) and cognitive impairment (SIDAM score). A logistic model was used when the Rankin score and the average MTR value. The average MTR of NAGM was significantly lower for individuals with CADASIL than for healthy control subjects ($P < 0.0001$). The average values of MTR histogram-derived measures from whole brain and NABT for individuals with CADASIL and control subjects are reported in Table 3. All MR values ranging from 0.52 to 0.79, $P$ values ranging from 0.002 to 0.0001, with the exception of those obtained from the NAWM of the infratentorial structures (a significance trend was found for the MTR values of the pons) and those from the NAGM of the occipital cortex. Average lesion MTR in individuals with CADASIL was significantly lower than the average MTR from all the NAWM regions studied ($P < 0.0001$). The average values of MTR histogram-derived measures from whole brain and NABT were significantly lower for individuals with CADASIL than for healthy control subjects ($P$ values ranging from 0.002 to 0.0001), with the exception of histogram peak heights. In individuals with CADASIL, the average MTR value from NABT was higher than that from the whole brain ($P = 0.003$). The average MTR of NAWM was correlated with average lesion MTR. The average MTR of NAGM was correlated only with average lesion MTR ($r = 0.46, P < 0.007$) (Table 4).

### Results

All CADASIL individuals showed hyperintense PD-weighted and hypointense T1-weighted abnormalities. Mean lesion volumes were 70.5 mL (range 5.1 to 174.0 mL) on PD-weighted scans and 14.7 mL (range 0.1 to 65.7 mL) on T1-weighted scans.

Average MTR values from ROIs placed in the NAWM and NAGM of individuals with CADASIL and healthy control subjects are reported in Tables 1 and 2. All values were significantly lower for individuals with CADASIL ($P$ values ranging from 0.01 to 0.0001), with the exception of those obtained from the NAWM of the infratentorial structures (a significance trend was found for the MTR values of the pons) and those from the NAGM of the occipital cortex. Average lesion MTR in individuals with CADASIL was significantly lower than the average MTR from all the NAWM regions studied ($P < 0.0001$). The average values of MTR histogram-derived measures from whole brain and NABT for individuals with CADASIL and control subjects are reported in Table 3. All MTR histogram-derived measures from whole brain and NABT were significantly lower for individuals with CADASIL than for healthy control subjects ($P$ values ranging from 0.002 to 0.0001), with the exception of histogram peak heights. In individuals with CADASIL, the average MTR value from NABT was higher than that from the whole brain ($P = 0.003$). The average MTR of NAWM was correlated ($r$ values ranging from 0.52 to 0.79, $P$ values ranging from 0.002 to <0.0001) with PD and T1 lesion volumes as well as with average lesion MTR. The average MTR of NAGM was correlated only with average lesion MTR ($r = 0.46, P < 0.007$) (Table 4).

### Table 1. MTR From ROIs Placed in PD-Visible Lesions and NAWM Regions of 33 Individuals With CADASIL and 12 Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>MTR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CADASIL</td>
</tr>
<tr>
<td>PD-visible lesions</td>
<td>39.0±2.8</td>
</tr>
<tr>
<td>All NAWM regions</td>
<td>41.9±1.3</td>
</tr>
<tr>
<td>Pons NAWM</td>
<td>44.4±1.9</td>
</tr>
<tr>
<td>Cerebellar hemisphere NAWM</td>
<td>42.5±1.6</td>
</tr>
<tr>
<td>Internal capsule NAWM</td>
<td>40.7±2.0</td>
</tr>
<tr>
<td>Periventricular NAWM</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>40.7±2.0</td>
</tr>
<tr>
<td>Posterior</td>
<td>42.8±1.8</td>
</tr>
<tr>
<td>Subcortical NAWM</td>
<td>40.5±2.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD. A 2-tailed Student t test was used for nonpaired data. For further details, see the text.

### Table 2. MTR From ROIs Placed in PD-Visible Lesions and NAGM Regions of 33 Individuals With CADASIL and 12 Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>MTR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CADASIL</td>
</tr>
<tr>
<td>PD-visible lesions</td>
<td>39.0±2.8</td>
</tr>
<tr>
<td>All NAGM regions</td>
<td>38.6±2.4</td>
</tr>
<tr>
<td>Caudate NAGM</td>
<td>35.5±2.3</td>
</tr>
<tr>
<td>Putamen NAGM</td>
<td>38.8±2.3</td>
</tr>
<tr>
<td>Thalamus NAGM</td>
<td>36.8±3.3</td>
</tr>
<tr>
<td>Frontal cortex NAGM</td>
<td>38.7±3.2</td>
</tr>
<tr>
<td>Temporal cortex NAGM</td>
<td>38.1±3.9</td>
</tr>
<tr>
<td>Parietal cortex NAGM</td>
<td>40.0±3.0</td>
</tr>
<tr>
<td>Occipital cortex NAGM</td>
<td>41.8±2.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD. A 2-tailed Student t test was used for nonpaired data. For further details, see the text.

### Table 3. MTR Histogram-Derived Measures From Whole Brain and NABT of 33 Individuals With CADASIL and 12 Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>MTR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CADASIL</td>
</tr>
<tr>
<td>Whole brain</td>
<td></td>
</tr>
<tr>
<td>Average MTR, %</td>
<td>39.5±1.5</td>
</tr>
<tr>
<td>Peak height</td>
<td>98.1±14.9</td>
</tr>
<tr>
<td>Peak location, %</td>
<td>34.3±1.7</td>
</tr>
<tr>
<td>NABT</td>
<td></td>
</tr>
<tr>
<td>Average MTR, %</td>
<td>39.7±1.3</td>
</tr>
<tr>
<td>Peak height</td>
<td>97.3±13.5</td>
</tr>
<tr>
<td>Peak location, %</td>
<td>34.3±1.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD. A 2-tailed Student t test was used for nonpaired data. For further details, see the text.

### Table 4. Correlations Between Average MTR of NAWM and NAGM and Macroscopic Lesion Extent and Severity in 33 Individuals With CADASIL

<table>
<thead>
<tr>
<th></th>
<th>Average MTR of NAWM</th>
<th>Average MTR of NAGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>PD hyperintense lesion volume</td>
<td>−0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>T1 hypointense lesion volume</td>
<td>−0.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average lesion MTR</td>
<td>0.79</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Statistical analysis was by Spearman rank correlation coefficient. For further details, see the text.
In Table 5, the correlations between average MTR values from NAWM, NAGM, NABT, lesions, and whole brain and age, Rankin score, and SIDAM score from individuals with CADASIL are reported. Apart from NAGM, the average MTR from all other tissues studied significantly decreased with increasing age, increasing Rankin score, and decreasing SIDAM score (r values ranging from 0.42 to 0.59, P values ranging from 0.01 to 0.0001). The multivariate analysis showed that average lesion MTR was associated with both the Rankin (P=0.03, corrected for age) and the SIDAM (P=0.02, corrected for age) scores. All the other tested variables were excluded from the 2 models.

Discussion

The present study shows that PD lesions in individuals with CADASIL have variable degrees of tissue destruction and that brain tissue outside PD abnormalities (both gray and white matter) is also damaged. It also shows that the overall lesion burden in CADASIL increases with age, degree of physical disability, and severity of cognitive impairment.

Our results indicate that MTR values from supratentorial NAWM are significantly lower in individuals with CADASIL than in normal subjects. The presence of white matter pathology beyond the resolution of conventional imaging differentiates CADASIL from other disorders of the central nervous system, including subcortical atherosclerotic encephalopathy, systemic immune-mediated disease, Devic’s neuromyelitis optica, and migraine. In all these conditions, previous MTI studies did not detect any significant changes outside PD-visible lesions. On the other hand, however, changes at a microscopic level can also be detected by MTI in the NAWM of patients with hydrocephalus, multiple sclerosis, amyotrophic lateral sclerosis, brain metastases, diffuse axonal injury, and neuropsychiatric systemic lupus erythematosus. Some of the latter conditions may also be in differential diagnosis with CADASIL. NAWM damage is less prominent in the infratentorial regions of individuals with CADASIL, where MTR values did not significantly differ from those of healthy control subjects. This finding confirms and extends previous studies using conventional MRI, which showed PD infratentorial lesions to be relatively rare in individuals with CADASIL and may also have important diagnostic implications. CADASIL and multiple sclerosis indeed have similar patterns of PD-weighted abnormalities, but infratentorial NAWM has significantly lower MTR in patients with multiple sclerosis than in control subjects. The nature and origin of the subtle changes in the NAWM from individuals with CADASIL remain subject to speculation. Low MTR values correlate with histopathologic findings of myelin loss and axon destruction, but edema and inflammation can also result in slightly decreased MTR values. Considering that vasogenic edema may occur in CADASIL and that edema of sufficient severity or duration can lead to myelin loss, the most tempting explanation is that demyelination is the likely substrate of the MTR changes that we found in the NAWM. However, we also found strong correlations between average MTR of the NAWM and PD lesion volume, T1 lesion volume, and average lesion MTR. This suggests that walle- rian degeneration secondary to axonal injury within severely damaged PD-visible lesions might, at least partially, contrib- ute to the NAWM changes that we detected.

MTR values from ROIs occurring in different gray matter structures of individuals with CADASIL were also reduced compared with those of normal control subjects. In individuals with CADASIL, MTR values from the NAGM might have been reduced by partial volume averaging from enlarged CSF spaces, because of the possible presence of cortical atrophy; however, we believe that the differences we found were not driven by such an effect for 2 reasons. First, MTR reductions were not limited to cortical regions, but they were also found in deep gray matter regions. Second, our analysis was carefully conducted by using a small ROI size to minimize partial volume averaging. Our findings agree with previous pathological reports showing the presence of subtle cortical changes, such as neuronal rarefaction and fibrillary gliosis, in individuals with CADASIL. Interestingly, MTR of the NAGM was found to be normal in patients with subcortical atherosclerotic encephalopathy, who have conventional MRI abnormalities similar to those found with CADASIL. Admittedly, the role of subtle white and gray matter pathology in CADASIL warrants further elucidation. However, its assessment might be important in the screening of asymptomatic individuals, or its change over time might be used as an earlier marker of disease evolution in longitudinal studies.

Previous studies have attempted to quantify the severity of lesion changes in individuals with CADASIL by measuring
the volume of hypointense lesions on T1-weighted scans.\textsuperscript{7,11} Although areas of hypointense signal on T1-weighted images correspond to areas where demyelination, axonal loss, and prominent reactive gliosis have occurred,\textsuperscript{44} the assessment of these abnormalities is highly operator dependent and does not provide a quantitative measure of tissue damage within individual lesions. On the contrary, MTR is a quantitative and operator-independent measure, which has been shown to correlate strongly with the degree of axonal and myelin loss.\textsuperscript{40} We have found that average lesion MTR from individuals with CADASIL is markedly decreased compared with NAWM-MTR and that average lesion MTR varies greatly from patient to patient. In conjunction with variable lesion extent and location,\textsuperscript{11} our findings indicate that variable severity of intrinsic lesion pathology may also contribute to the known variability of the clinical manifestations of CADASIL.\textsuperscript{5,10} This further argues in favor of a quantitative approach to monitor CADASIL evolution that is either natural or modified by treatment.

In the present study, we obtained MTR histograms of the whole-brain tissue. MTR histogram analysis allows evaluation of data from all the image pixels of the brain tissue, thus providing a complete assessment of CADASIL pathology, including PD-visible lesions, NAWM, and NAGM. We also obtained MTR histograms of the NABT only, by accurately removing from the coregistered MTR maps all the pixels known to belong to PD-visible lesions. We found that (1) average MTR values and peak locations of the histograms were significantly lower in individuals with CADASIL than in control subjects, and (2) in individuals with CADASIL, average MTR of whole-brain tissue was significantly lower than that of NABT. This confirms that most of the brain tissue is affected in CADASIL and that CADASIL pathology is more severe within rather than outside PD-visible lesions. Interestingly, the peak heights of the whole-brain and NABT histograms were not significantly different between control subjects and individuals with CADASIL. MTR histogram peak height is considered a measure of the amount of tissue at “truly” normal MTR values.\textsuperscript{12,15,23} As a consequence, our findings suggest that changes in the brain of individuals with CADASIL, although severe enough to determine a reduction of average MTR values and peak locations of the histograms, are not diffuse enough to result in a reduction of the peak height. Clearly, with such an approach, information related to the status of specific brain structures or tissues is lost. However, the demonstration that MTR histogram-derived metrics are sensitive measures of tissue damage in CADASIL is important, considering the relatively large number of affected individuals (120 European CADASIL families have been identified in the last few years) and the potential for effective treatments.\textsuperscript{7} In the context of clinical trials, it may be unfeasible to measure MTR changes from several different brain regions and tissues, and such an analysis is potentially difficult to interpret. A quantitative measure reflecting overall lesion burden, such as average MTR from whole-brain tissue, might be more desirable and represent a useful additional outcome measure.

We also investigated correlations between MTI changes and clinical characteristics in CADASIL. We found that increasing age is significantly correlated with decreasing average MTR from all the tissues studied apart from NAGM. This confirms and extends previous observations,\textsuperscript{7,9,11} showing that increasing age is associated not only with increasing total lesion volumes but also with increased tissue damage within and outside such lesions. Using univariate correlation analysis, we also found that MTR values from NAWM, NABT, lesions, and whole-brain tissue are significantly correlated with physical disability and cognitive impairment. In addition, multivariate analysis showed that average lesion MTR is the single most relevant MTR quantity correlated with both these clinical measures of disease severity. These findings suggest that the amount and the severity of the affected brain tissue are critical factors in determining the clinical status in CADASIL. The correlations found between MTI-derived metrics and the clinical manifestations of CADASIL indicate the potential for quantitative MR techniques in monitoring the evolution of CADASIL.

Acknowledgments

We are grateful to Dr M.P. Sormani for her help in conducting the statistical analysis and to Dr M.A. Horsfield for revising the manuscript language.

References

7. Dichgans M, Filippi M, Brüning R, Iannucci MTI in CADASIL 647


Correlations Between Clinical Findings and Magnetization Transfer Imaging Metrics of Tissue Damage in Individuals With Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy


*Stroke*. 2001;32:643-648
doi: 10.1161/01.STR.32.3.643

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 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/32/3/643

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/