Callosal Atrophy in Patients With Lacunar Infarction and Extensive Leukoaraiosis
An Indicator of Cognitive Impairment

Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; Masafumi Ogawa, MD; Yasuomi Ouchi, MD; Jun Kimura, MD

Background and Purpose It is unclear why only some patients with lacunar infarction and radiological evidence of diffuse white matter abnormalities have dementia. The purpose of this study is to investigate the value of callosal atrophy as an indicator of cognitive impairment.

Methods We used magnetic resonance imaging to evaluate 11 right-handed male patients with lacunar infarction and extensive white matter hypodensities on computed tomography (8 with dementia and 3 without dementia). The midsagittal corpus callosum area on T1-weighted images was compared with the IQ determined by the Wechsler Adult Intelligence Scale. The relation between these parameters and cerebral oxygen metabolism measured with positron emission tomography was also evaluated in the 8 patients with dementia.

Results All patients showed diffuse high-intensity areas in the bilateral hemispheric white matter on T1-weighted images. Compared with 19 age- and sex-matched right-handed normal control subjects, the patients had a significantly smaller callosal area. The severity of callosal atrophy, which varied from mild to severe, was significantly related to the total IQ. In the 8 demented patients, the total callosal area was significantly correlated with the mean level of oxygen metabolism in the cerebral white matter.

Conclusions In patients with lacunar infarction and diffuse white matter abnormalities, the presence of callosal atrophy may indicate cognitive impairment. Callosal atrophy may reflect the severity and extent of white matter damage associated with a decrease in oxygen metabolism, which may determine the severity of intellectual decline. (Stroke. 1994;25:1788-1793.)

Key Words • cerebrovascular disorders • dementia • magnetic resonance imaging • tomography, emission computed
The number of pixels that had signal intensities corresponding to white matter regions of interest on the MR images at the same level set for the region of interest was ware for image analysis was programmed by a member of our research team. Each magnetic resonance (MR) image was recorded with a video camera and digitized by the image computer-assisted image analyzer (FDM98-1; Photron) and a midsagittal images were quantitatively analyzed with a com- puter program that had previously been described in more detail.12

The specifications of our PET scanner have been reported elsewhere.13 In brief, the device has four rings containing 18F germinate detectors, and it provides seven tomographic slices with each scanning process. The device offers a best spatial resolution of 7.6 mm (full width at half maximum) at the center of the field and an axial resolution of 12 mm at the center. The scanning procedure was as follows. Before the study, a 68Ge/ 68Ga transmission scan was performed for 20 minutes to allow correction for attenuation. Cerebral blood flow (CBF) was determined while the subject continuously inhaled C14O2 through a mask at 370 to 555 MBq/min. Measurement of the cerebral metabolic rate of oxygen (CMRO2) and the oxygen extraction fraction (OEF) required continuous inhalation of O2 at 0.74 to 1.11 GBq/min. Data were collected for 5 minutes. A single breath of 2.96 GBq of C14O2 was used to measure the cerebral blood volume (CBV). We calculated CBF, CMRO2, and OEF based on the steady-state method.14 CMRO2 and OEF were corrected by the CBV.14 Functional images were reconstructed 64x64 pixels, with each pixel representing 2.5x2.5 mm.

We analyzed three tomographic planes that were located 5.0, 6.6, and 8.2 cm above and parallel to the orbitomeatal line, corresponding to the level of the basal ganglia and thalamus, the body of the lateral ventricle, and the centrum semiovale, respectively. Regions of interest were set on the bilateral cerebral cortical areas and white matter (Fig 1). To determine the cortical regions of interest, each image was examined by placing a total of 16 to 18 circular regions of interest 10 mm in diameter on the cortical rim of each hemisphere. The slice 6.6 cm above the orbitomeatal line was used to determine the regions of interest in the white matter. A circular region of interest 15 mm in diameter was placed on the frontal and parieto-occipital white matter anterolateral and posterolateral to the lateral ventricle, respectively. We placed the white matter regions of interest on the MR images at the same level

### Table 1. Cognitive Impairment in 11 Patients With Lacunar Infarction and Extensive Leukoaraiosis

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age, y</th>
<th>Dementia</th>
<th>HDRS</th>
<th>WAIS-T</th>
<th>WAIS-V</th>
<th>WAIS-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>None</td>
<td>29.5</td>
<td>107</td>
<td>109</td>
<td>104</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>None</td>
<td>27.5</td>
<td>95</td>
<td>101</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>None</td>
<td>24</td>
<td>74</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Mild</td>
<td>19.5</td>
<td>81</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>Mild</td>
<td>6</td>
<td>78</td>
<td>64</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>Mild</td>
<td>16</td>
<td>69</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Mild</td>
<td>24</td>
<td>64</td>
<td>71</td>
<td>&lt;60</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>Mild</td>
<td>18.5</td>
<td>60</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>Moderate</td>
<td>8</td>
<td>&lt;60</td>
<td>&lt;60</td>
<td>&lt;60</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>Moderate</td>
<td>5</td>
<td>&lt;60</td>
<td>60</td>
<td>&lt;60</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>Severe</td>
<td>0</td>
<td>&lt;60</td>
<td>&lt;60</td>
<td>&lt;60</td>
</tr>
</tbody>
</table>

Pt indicates patient; HDRS, Hasegawa Dementia Rating Scale; WAIS-T, total intelligence score on the Wechsler Adult Intelligence Scale; V, verbal test; and P, performance test.
The mean values for the cerebral cortex and white matter were calculated as the average of all the cortical and subcortical regions, respectively. As on the PET images by a method of correlating PET with MRI that has been described elsewhere. The mean CMRO₂ values for the cerebral cortex were calculated as the average of the values for all regions of interest in the bilateral cerebral cortical areas of three images, weighted by region size. The mean CMRO₂ values for the white matter were also calculated as the average of the values for four regions of interest in the bilateral white matter areas.

Repeated-measures ANOVA was performed for the partial area measurements of the corpus callosum to assess whether the relation between patients and control subjects differs across regions. Then we compared the callosal areas of the patients and control subjects by Student's t test to detect regional differences. Statistical significance was indicated by P < .01 with Bonferroni's correction for multiple comparisons. Linear regression was used to analyze the relation between callosal area and the WAIS IQ. In the 8 patients with dementia, we also analyzed the relation of the mean CMRO₂ value for the cerebral cortex or white matter to WAIS IQ and callosal area by means of partial correlation coefficients. The WAIS IQ of less than 60 was arbitrarily assigned to 59.

All patients showed similar diffuse, high signal intensity areas in the bilateral hemispheric white matter on T₂-weighted images (Fig 2). These high-intensity areas involved almost the entire white matter of the corona radiata and centrum semiovale as well as the frontal and parietotemporo-occipital subcortical white matter. In contrast, only a few high-intensity areas were found in the corpus callosum. All of the patients also had multiple small, high-intensity lesions in the basal ganglia and/or thalamus.

Repeated-measures ANOVA showed a significant interaction between the callosal region and the diagnostic classification (P < .0001), indicating that the relation between patients and control subjects differs across regions. The patients showed a significant decrease in the areas of all regions of the corpus callosum compared with the control subjects, with atrophy being most severe in the midanterior portion (Table 2). Callosal atrophy varied from mild to severe in the patients (Fig 2), and the total area of the corpus callosum was significantly correlated with the total IQ (Fig 3), verbal IQ (r = .781, P < .005), and performance IQ (r = .618, P < .05).

In the 8 patients with dementia, the mean oxygen metabolism values for the white matter were roughly proportional to those of the cerebral cortex (r = .579, P = .1324). However, 2 patients showed disproportionate hypometabolism in the white matter. The total IQ was significantly correlated with the mean level of oxygen metabolism in the white matter but not with that in the cerebral cortex (using the value for the cerebral cortex or the white matter as the variable to be controlled) (Fig 4). The verbal IQ was also correlated only with the
mean level of oxygen metabolism in the white matter ($p=.77, P<.05$), but the performance IQ was not. The mean level of oxygen metabolism in the white matter was also correlated with the size of the corpus callosum, but metabolism in the cerebral cortex was not (using the value for the cerebral cortex or the white matter as the variable to be controlled) (Fig 5). The patients’ age was not related to either the callosal area or the CMRO$_2$ value.

**Discussion**

This study shows that atrophy of the corpus callosum occurs in association with intellectual decline in patients with lacunar infarction and radiological evidence of diffuse white matter abnormalities and that this atrophy is related to the severity of white matter damage. Callosal atrophy may reflect the pathology that directly produces cognitive impairment, because all the patients showed a similar extent of white matter abnormalities on T$_2$-weighted MRI images. In contrast to the severe hemispheric white matter abnormalities, only a few high-intensity areas were found in the corpus callosum itself, and the cortical structures were well preserved in all cases. Therefore, the major cause of callosal atrophy in these patients did not seem likely to be ischemic damage and was probably axonal degeneration arising from subcortical lesions. The corpus callosum is relatively resistant to hypoperfusion and is generally spared inBinswanger’s disease.\textsuperscript{17} Because the severity of nerve fiber damage may not be affected by the direction of the fibers,\textsuperscript{18} callosal atrophy may reflect the severity and extent of axonal disruption by white matter changes throughout the cerebrum, which determine the severity of cognitive impairment. In our patients, callosal atrophy was most severe in the midanterior portion, suggesting that the white matter of the upper frontal region was most severely damaged. Thus, the distribution of callosal atrophy may also reflect the pattern of white matter damage.

Some factors other than white matter damage may contribute to callosal atrophy in subjects with radiological evidence of white matter abnormalities. Size of the corpus callosum varies in the normal population. In addition, risk factors for stroke may be related to the severity of corpus callosum atrophy. For example, hypertension is reported to be associated with brain atrophy,\textsuperscript{19} suggesting that hypertensive subjects may have small corpora callosa. These factors might lead to a weak correlation between callosal size and cognitive function in a larger patient sample. In that situation, longitudinal studies should be done to determine whether rate of callosal atrophy is correlated with rate of cognitive deterioration.

Only a few studies have demonstrated atrophy of the corpus callosum in vascular dementia\textsuperscript{20} or Binswanger's disease.\textsuperscript{21} One qualitative MRI study of lacunar infarction\textsuperscript{20} showed that demented patients had significantly more extensive atrophy of the corpus callosum and more severe leukoaraiosis than nondemented patients. Electron microscopic examination of seven postmortem brains with diffuse myelin pallor from patients with Binswanger's disease showed a decrease of nerve fibers in the anterior part of the corpus callosum.\textsuperscript{21} However, the actual significance of callosal atrophy in Binswanger's disease has been unclear. Our study suggests that callosal atrophy may be related to the process that determines the severity of dementia in this disease.

In Binswanger's disease, cognitive impairment may depend on the severity and extent of damage to the white matter, because the white matter is mainly affected and the cerebral cortex appears relatively

![Fig 3](image3.png)

**Fig 3.** Scatterplot relates the total area of the corpus callosum to the Wechsler Adult Intelligence Scale (WAIS) total IQ. The symbol $\bullet$ indicates an IQ of $<60$, which was assigned to 59.

![Fig 4](image4.png)

**Fig 4.** Scatterplot relates the Wechsler Adult Intelligence Scale (WAIS) total IQ to the mean level of oxygen metabolism in the white matter. The symbol $\bullet$ indicates an IQ of $<60$, which was assigned to 59. The $p$ value indicates the partial correlation coefficient obtained using the value for the cerebral cortex as the variable to be controlled.
of callosal atrophy may help to better define the role of white matter changes with associated cerebral dysfunction. Simultaneous evaluation of callosal atrophy may indicate axonal disruption by the lacunar infarction and radiological diffuse white matter abnormalities. This study was supported by scientific research grants C-05670556 and A-04404043 from the Japanese Ministry of Education, Science, and Culture and by the Japan Foundation for Aging and Health. We thank Professor Junji Konishi and his staff at the Department of Radiology and Nuclear Medicine, Faculty of Medicine, Kyoto University (Dr. Yoshiharu Yonekura, Hideo Saji, Reinin Asato, and Yasuhiro Magata), for their support and technical help. We also thank Drs Shinya Yamaguchi, Toshiki Doi, and Yasuhiro Nagahama for their cooperation.

References


Callosal atrophy in patients with lacunar infarction and extensive leukoaraiosis. An indicator of cognitive impairment.

H Yamauchi, H Fukuyama, M Ogawa, Y Ouchi and J Kimura

*Stroke*. 1994;25:1788-1793
doi: 10.1161/01.STR.25.9.1788

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 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/25/9/1788

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/