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

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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 T2-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 term "Binswanger's disease" refers to a form of dementia characterized histologically by the combination of multiple lacunes and extensive diffuse noncavitating degeneration of the white matter.1-4 These diffuse white matter abnormalities are easily visualized as diffuse low-density areas on computed tomography (CT) or as diffuse high-intensity areas on T1-weighted magnetic resonance imaging (MRI), and such changes were initially thought to be diagnostic of Binswanger's disease. However, not all patients with these radiological findings have dementia,5-6 and so what actually determines intellectual function in patients with diffuse white matter abnormalities remains unclear. There are no changes in attenuation or signal intensity that specifically indicate cognitive impairment. The corpus callosum is composed of interhemispheric fibers traversing the subcortical white matter. In patients with diffuse radiological abnormalities of the hemispheric white matter, atrophy of the corpus callosum may result from axonal disruption, and the extent of the atrophy may be related to cognitive impairment.

To investigate whether atrophy of the corpus callosum occurs in association with intellectual decline, we used MRI to quantitatively evaluate atrophy of the corpus callosum in patients with lacunar infarction and diffuse white matter abnormalities and examined its relation to intellectual function. In patients with dementia, we also correlated callosal size with white matter oxygen metabolism as determined by positron emission tomography (PET) to investigate whether callosal atrophy is related to the severity of white matter damage.

Subjects and Methods

Eleven consecutive right-handed men, aged 59 to 77 years (mean±SD, 67±6 years), who showed lacunar infarction and diffuse white matter abnormalities on CT were studied with MRI. All patients had a history of hypertension and minor stroke, and 2 patients also had diabetes mellitus. Hypertension was present in 6 patients on admission. Neurological examination showed gait disturbance in all patients, pseudobulbar palsy in 8, urinary incontinence in 7, mild motor paresis in 6, and emotional incontinence in 3. CT demonstrated extensive heterogeneous reduction of attenuation in the bilateral hemispheric white matter. Multiple small low-density areas were also seen in the basal ganglia and/or thalamus. No significant stenosis of the cervical or intracranial arteries was noted in any of the patients on conventional angiography. Other possible causes of diffuse white matter lesions (eg, demyelination, inflammation, or intoxication) were ruled out by clinical and laboratory investigations including cerebrospi-
right angles to a straight line through the inferior borders of the splenium and the rostrum were drawn at the anterior border of the rostrum and the caudal end of the splenium. The area between these two lines was then divided into quarters by three additional perpendicular lines to produce a total of four regions: the anterior, midanterior, midposterior, and posterior regions. The total and regional areas of the callosum were measured, and the absolute values were calculated by means of a reference scale of MR images. All measurements were performed by one investigator who was blinded to the clinical status of the patients. The predetermined intraobserver reliability was quite high (r=.99, P<.001).

The specifications of our PET scanner have been reported elsewhere. In brief, the device has four rings containing $^{18}$F uramate 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 $^{68}$Ge/ $^{68}$Ga transmission scan was performed for 20 minutes to allow correction for attenuation. Cerebral blood flow (CBF) was determined while the subject continuously inhaled $^{15}$O. A single breath of 2.96 GBq of $^{15}$O was used to measure the cerebral blood volume (CBV). We calculated CBF, CMRO$_2$, and OEF based on the steady-state method. Functional images were reconstructed $64 \times 64$ pixels, with each pixel representing $2.5 \times 2.5$ 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 vascular disease and 9 patients with mild cervical spondylosis. None of them exhibited any cerebral symptoms or any MRI abnormalities, except for a few small high-intensity lesions in the hypointense areas. We included 10 normal subjects who underwent a medical examination including MRI for the detection of asymptomatic brain disease and 9 patients with mild cervical spondylosis. None of them exhibited any cerebral symptoms or any MRI abnormalities, except for a small high-intensity lesion in the subcortical white matter on T$_1$-weighted images. Eight had hypertension, and 2 others had diabetes mellitus.

MRI was performed with a Signa unit (General Electric) operating at a field strength of 1.5 T. T$_1$-weighted sagittal images were obtained by means of a spin-echo pulse sequence (repetition time, 400 milliseconds; echo time, 20 milliseconds). Axial T$_1$-weighted images were also obtained with spin-echo pulse sequences (repetition time, 3000 millisecond; echo time, 40 and 80 milliseconds). The slice thickness was 3 mm for both types of images. Sections were contiguous in sagittal planes and had an intersection gap of 1.5 mm in axial planes.

To measure the extent of atrophy of the corpus callosum, mid sagittal images were quantitatively analyzed with a computer-assisted image analyzer (FDM98-1; Photron) and a personal computer (PC-9801; Nihon Electric Co). The software 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 analyzer using a 256 $\times$ 256 data matrix and a 64-step gray scale. The number of pixels that had signal intensities corresponding to the predetermined level set for the region of interest was then counted. There is some morphological variation of the corpus callosum, and the boundaries of the different parts of this structure are indistinct. Therefore, we arbitrarily divided each corpus callosum into four parts as follows: Two lines at

<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>
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<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.
FIG 1. Diagrams illustrate the circular regions of interest placed over the cerebral cortex and the white matter. 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 CMRO\textsubscript{2} 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 CMRO\textsubscript{2} 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 \( P < 0.01 \) 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 CMRO\textsubscript{2} 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.

Results

All patients showed similar diffuse, high signal intensity areas in the bilateral hemispheric white matter on T\textsubscript{2}-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 (\( P < 0.0001 \)), 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 = 0.781, \( P < 0.005 \)), and performance IQ (r = 0.618, \( P < 0.05 \)).

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 = 0.579, \( P = 0.1324 \)). 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 ($r=.77$, $P<.05$), 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 T2-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{15} 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} orBinswanger'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 non-demented 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 inBinswanger'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 in-

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**Table 2. Areas of the Four Regions of the Corpus Callosum In Control Subjects and Patients**

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>MAP</th>
<th>MPP</th>
<th>PP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects (n=19)</td>
<td>2.04±0.24</td>
<td>1.01±0.14</td>
<td>0.84±0.20</td>
<td>2.02±0.33</td>
<td>5.92±0.79</td>
</tr>
<tr>
<td>Patients (n=11)</td>
<td>1.51±0.28*</td>
<td>0.66±0.17*</td>
<td>0.59±0.14t</td>
<td>1.51±0.38t</td>
<td>4.29±0.84*</td>
</tr>
<tr>
<td>% of control value</td>
<td>73.9</td>
<td>65.4</td>
<td>71.0</td>
<td>74.8</td>
<td>72.4</td>
</tr>
</tbody>
</table>

*P<.0001, tP<.001, #P<.002 vs control subjects by Student's t test.

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

**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 • indicates an IQ of $<60$, which was assigned to 59. The $r$ 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 with a decrease in oxygen metabolism, which may indicate axonal disruption by the abnormalities on CT or T2-weighted MRI may not have any specific meaning per se. However, the coexistence of callosal atrophy may indicate the severity of cognitive impairment, while that of the cerebral cortex was not. Thus, cognitive impairment inBinswanger's disease may depend on a decrease of white matter oxygen metabolism. The association between metabolic depression and callosal atrophy suggests that the reduction in oxygen metabolism may parallel irreversible damage of the white matter with a decrease in nerve fibers. Although a decrease of oxygen metabolism has been demonstrated in the cerebral cortex as well as the white matter, hypometabolism of the latter region predominates and cortical hypometabolism probably results from deafferentation when the preservation of cortical structures is considered. In our patients with dementia, white matter oxygen metabolism was roughly proportional to the level of cortical hypometabolism, supporting this hypothesis, although two patients showed white matter hypometabolism that was out of proportion to the changes in the cortex. In addition, the decrease of white matter oxygen metabolism was correlated with the severity of cognitive impairment, while that of the cerebral cortex was not. Thus, cognitive impairment in Binswanger's disease may depend on a decrease of white matter oxygen metabolism. The association between this metabolic depression and callosal atrophy may suggest that the reduction in oxygen metabolism in the cerebral cortex was not.

Primary lesions of the corpus callosum cause functional impairment of interhemispheric transfer, i.e., the callosal disconnection syndrome. In multiple sclerosis, which selectively impairs the white matter, callosal atrophy is associated with abnormalities of tests exploring the interhemispheric transfer of information. However, callosal transaction does not irreversibly reduce intellectual function or cortical glucose metabolism. Therefore, callosal atrophy is not the primary factor causing intellectual impairment in Binswanger's disease but instead is a manifestation of hemispheric white matter change that results in cognitive dysfunction.

We conclude that atrophy of the corpus callosum is associated with intellectual decline in patients with lacunar infarction and radiological diffuse white matter abnormalities. Corpus callosum atrophy may reflect the severity and extent of white matter damage associated with a decrease in oxygen metabolism, which may determine the severity of cognitive impairment in patients with Binswanger's disease. Diffuse white matter abnormalities on CT or T2-weighted MRI may not have any specific meaning per se. However, the coexistence of callosal atrophy may indicate axonal disruption by the white matter changes with associated cerebral dysfunction and cognitive impairment. Simultaneous evaluation of callosal atrophy may help to better define the role of radiological white matter lesions in cognitive decline, but this hypothesis should also be tested in patients with less marked white matter abnormalities.

Acknowledgments

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References


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