Atrophy of the Corpus Callosum, Cortical Hypometabolism, and Cognitive Impairment in Corticobasal Degeneration

Hiroshi Yamauchi, MD, PhD; Hidenao Fukuyama, MD, PhD; Yasuhiro Nagahama, MD, PhD; Yukinori Katsumi, MD; Yun Dong, MD; Takuya Hayashi, MD; Junji Konishi, MD, PhD; Jun Kimura, MD

Objective: To investigate whether atrophy of the corpus callosum is associated with cognitive impairment and cerebral cortical hypometabolism in corticobasal degeneration.

Design: Prospective clinicoradiological correlation with magnetic resonance imaging and positron emission tomography.

Setting: A university hospital.

Patients: Eight right-handed patients with clinically diagnosed corticobasal degeneration (mean±SD age, 64±8 years).

Main Outcome Measures: Midsagittal corpus callosum area–skull area ratio (on T1-weighted magnetic resonance images), the sum of the scaled scores of the 6 subtests on the Wechsler Adult Intelligence Scale–Revised (Digit Span, Arithmetic, Picture Arrangement, Object Assembly, Block Design, and Digit Symbol), and cerebral metabolic rate of glucose (measured with positron emission tomography by using fludeoxyglucose F 18 as a tracer).

Results: Compared with 36 age-matched right-handed control subjects, the patients had significantly decreased callosal area–skull area ratio. The reduction in this ratio was greatest in the middle half of the corpus callosum. The atrophy of the corpus callosum was accompanied by a decreased mean cortical glucose metabolic rate with hemispheric asymmetry and a decrease in the sum of the scaled subtest scores of the Wechsler Adult Intelligence Scale–Revised.

Conclusions: Atrophy of the corpus callosum with middle predominance is present in corticobasal degeneration, and this atrophy is associated with cognitive impairment and cerebral cortical hypometabolism with hemispheric asymmetry. Atrophy of the corpus callosum might reflect the severity of the disconnection between cortical regions, and this may be an important factor in the development of cerebral cortical dysfunction in corticobasal degeneration.

Arch Neurol. 1998;55:609-614

Corticobasal degeneration (CBD) is a neurodegenerative disorder with a distinctive asymmetrical akinetic-rigid syndrome in which cerebral cortical signs are the characteristic features. The clinical presentation of cortical dysfunction ranges from the localized cortical signs, including apraxia, cortical sensory loss, alien hand signs, and cortical reflex myoclonus, to generalized cognitive disturbance. Although these cortical signs may be the result of the involvement of specific regions that are important for higher cerebral functions, the mechanisms of cerebral cortical dysfunction in this disease are not completely clarified.

Pathological studies in CBD have disclosed marked neuronal loss and gliosis in layers 2 and 3 of the cerebral cortex, the distribution of which varies from the focal frontoparietal region to more extensive cortical areas. Layer 3 includes pyramidal cells that project long association fibers connecting intrahemispheric cortical regions and commissural fibers connecting bilateral cortical regions through the corpus callosum. Therefore, damage to layer 3 in CBD would impair large-scale networks among cerebral cortical regions that are indispensable to the performance of complex cortical functions. The extent of the atrophy of the corpus callosum, which might parallel the overall loss of long association and commissural fibers, may reflect the degree of disconnection among cortical regions, potentially contributing to the impression of cerebral cortical dysfunction in CBD.

The objective of this study was to investigate whether atrophy of the corpus callosum is present in CBD and, if so,
PATIENTS AND METHODS

PATIENTS

We studied 8 right-handed patients with a clinical diagnosis of CBD with magnetic resonance imaging (MRI) and positron emission tomography (PET). These patients were 2 men and 6 women (age range, 49-74 years; mean±SD age, 64±8 years). The diagnosis of CBD was made clinically on the basis of the insidious onset and gradual progression of an ataxic akinetic-rigid syndrome with cerebral cortical signs, such as apraxia, cortical sensory loss, alien hand signs, and cortical reflex myoclonus. All patients exhibited marked asymmetry in their clinical signs. None of them had any history of medical or psychiatric disorder. None exhibited vertical supranuclear palsy with downward gaze abnormalities, dysautonomia, hallucination, or limb ataxia. None had initial symptoms of balance and gait disturbance or dementia. The response to levodopa and dopamine agonists had been poor in all cases. In all patients, the possibility of space-occupying lesions and cerebrovascular lesions was excluded by MR imaging, which disclosed only a few high-intensity spots in the subcortical white matter on T2-weighted images. All patients had normal laboratory test results, including serological tests for syphilis, cyanocobalamin levels, and thyroid hormone levels. The duration of illness was 40±17 months (range, 13-66 months). The time of onset of the disease was determined from the patients’ recollection of when the first symptoms occurred. The clinical data are summarized in Table 1. All but one of the patients were studied with all subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R). We calculated the sum of the scaled scores of the 6 subtests that were sensitive to brain injury (Digit Span, Arithmetic, Picture Arrangement, Object Assembly, Block Design, and Digit Symbol) as a measure of cognitive function. For each patient, all of the MR imaging, PET, and neuropsychological evaluations were performed within 2 weeks.

We also studied, by MR imaging, 36 age- and sex-matched right-handed control subjects, 9 men and 27 women, aged 49 to 74 years (mean±SD, 64±8 years). They included 8 normal subjects who underwent a neurological examination including MR imaging for the detection of asymptomatic brain disease and 31 subjects who underwent MR imaging because of headache or dizziness. All of these subjects showed normal neurological findings and no specific neurological diseases other than tension-type headache. None exhibited any abnormal MR imaging findings, except for a few high-intensity spots in the subcortical white matter on T1-weighted images. They also had no history of medical or psychiatric disorder.

RESULTS

There was a significant interaction between the callosal region and the diagnostic classification (P<.001, repeated-measures analysis of variance), indicating that the relationship between patients and controls differed across regions. In the regional analysis, the callosal area–skull area ratios in the patients were significantly lower than those in the control subjects in all regions of the corpus callosum (Table 2). The severity of atrophy showed the following order: middle-posterior>middle-anterior>anterior>posterior region. An overlap between the total callosal–skull area ratio in the patients and that in the controls was found in only 1 patient.

In the patients, callosal atrophy was correlated with decreased cerebral cortical glucose metabolism (Figure 1). The total callosal area–skull area ratio was...
of the lateral ventricles was quantitatively analyzed in a similar way. The level that was set for the lateral ventricles was determined as the range from the minimum value to the mean value of the maximum and minimum values minus 1, where the maximum value was the maximum pixel value of the surrounding white matter, and the minimum value was the minimum pixel value of the lateral ventricles. We also measured the areas of the axial internal skull surfaces by tracing the inner table and calculated, separately for each hemisphere, the lateral ventricular area–skull area ratio (a percentage).

In the measurement of the extent of atrophy of the cerebral cortex, the T1-weighted axial section through the image containing the centrum semiovale was analyzed. We measured the area of the subarachnoid space. The level that was set for the subarachnoid space was determined as the range from the minimum value to the mean value of the maximum and minimum values minus 1, where the maximum value was half the value of the maximum pixel value of the hemispheric white matter and the minimum value was the minimum pixel value of the subarachnoid space. The subarachnoid space area–skull area ratio (a percentage) was calculated separately for each hemisphere.

All measurements were performed by 1 investigator (H.Y.) who was unaware of the clinical status of the patients. Before this study, the observer reliability of our procedure was evaluated in 20 subjects with or without neurological diseases. There was high intraobserver reliability for the measurement of callosal area–skull area ratio, lateral ventricular area–skull area ratio, and subarachnoid space area–skull area ratio ($r=0.98, P<.001$; $r=0.99, P<.001$; and $r=0.98, P<.001$, respectively).

**POSITRON EMISSION TOMOGRAPHY**

Patients were allowed a light breakfast 6 hours before PET study. All antiparkinsonian drug therapy was discontinued for at least 9 hours before scanning. Written informed consent was obtained from each patient under the guidance of the Ethics Committee of the Kyoto University Faculty of Medicine, Kyoto, Japan. Scans were performed on all patients with the use of a commercially available PET system (PCT-3600W; Hitachi Medical Co, Tokyo, Japan). This system simultaneously acquires 15 slices with a center-to-center distance of 7 mm. All scans were obtained at a resolution of a 7.5 mm full-width half-maximum in the transaxial direction and 6.5 mm in the axial direction in the wobbling mode. Patients were positioned with the orbitomeatal line parallel to the detector rings. Examinations were performed on subjects with their eyes open and ears unplugged in a dimly lit room. After a transmission scan, each subject was intravenously infused with 166 to 281 MBq (4.5-7.6 mCi) of fludeoxyglucose F 18. Arterial blood samples were withdrawn just after administration, at 15, 30, 45, 60, 75, and 90 seconds, and at 2, 3, 4, 6, 8, 10, 15, 20, 30, 45, and 60 minutes. The PET scan was started 40 minutes after fludeoxyglucose injection, and emission data were collected for 20 minutes. The reconstructed image consisted of 128×128 pixels, with each pixel measuring 2.0×2.0 mm. The cerebral metabolic rate of glucose (CMRGlc) was calculated by Phelps’ autoradiographic method, using fixed values of $K1^*=0.102$, $k2^*=0.130$, $k3^*=0.062$, and $k4^*=0.0068$ for the rate constants and 0.42 for the lumped constant.

We analyzed 6 tomographic planes, 43, 50, 57, 64, 71, and 78 mm above and parallel to the orbitomeatal line, which corresponded to the levels from the basal ganglia and thalamus to the centrum semiovale. Each image was examined by placing manually circular regions of interest (diameter, 12 mm) compactly over the gray matter of the cortex in each hemisphere. We used a method correlating PET with MR imaging described elsewhere. According to the atlas prepared by Kretschmann and Weinrich, the region of interest was included in the frontoparietal, parietotemporal, temporal, and occipital cortices and the peritendinous sensorimotor and primary visual cortex. The mean hemispheric and cortical CMRGlc values were calculated as the average of all the regions of interest besides the primary visual cortex contained in each hemisphere and the bilateral hemispheres, respectively. Each was weighted by region size. We also calculated the asymmetry index (AI) between the right (R) and left (L) cerebral cortex as $AI$ (absolute % value)=$(|R−L|/R+L)×200$, where $|R−L|$ represents the absolute value of the difference between the right and left mean hemispheric CMRGlc values.

**STATISTICAL ANALYSES**

Repeated-measures analysis of variance was performed for the partial area measurements of the corpus callosum to assess whether the relationship between patients and controls differed across regions. We then compared the callosal area–skull area ratios of the patients and controls by Student $t$ test to detect regional differences, and significance was regarded at $P<.01$ with the use of Bonferroni correction for multiple comparisons. We used simple linear and stepwise regression analyses to analyze the relationships of the metabolic measures (the mean cortical CMRGlc value and the asymmetry index) or the sum of the scores of the 6 WAIS-R subtests to the callosal area–skull area ratio, the subarachnoid space area–skull area ratio, the ventricular area–skull area ratio, the age, and the duration of the disease. Significance was regarded at $P<.05$.

significantly correlated with the mean cortical CMRGlc value ($r=0.84, P<.01$) (Figure 2, top). None of the subarachnoid space area–skull area ratios and the ventricular area–skull area ratios were significantly related to the mean hemispheric CMRGlc value in the hemisphere contralateral to the more affected side of the body ($r=0.04, P=.92$, and $r=−0.34, P=.42$, respectively) or in the ipsilateral hemisphere ($r=−0.22, P=.61$, and $r=−0.39, P=.34$, respectively). In all patients, the mean hemispheric CMRGlc values for the cortex contralateral to the more affected side of the body were less than those for the ipsilateral cortex. A strong correlation was found between the mean hemispheric CMRGlc values for the cortex contralateral to the more affected side of the body and those for the ipsilateral cortex ($r=0.99, P<.001$). The total callosal area–skull area ratio was also negatively correlated with the asymmetry index of the hemispheric CMRGlc value ($r=−0.81, P<.02$) (Figure 2, bottom). Thus, patients with callosal atrophy showed asymmetrical and bilateral decrease in the CMRGlc value.
The degree of callosal atrophy was also correlated with the degree of cognitive deterioration (Figure 3). In the patients, the degree of cognitive impairment, as shown by a decrease in the sum of the scaled WAIS-R subtest scores, varied (Table 1). However, the total callosal area–skull area ratio showed a strong correlation with the sum of the subtest scores ($r=0.91$, $P<.005$). The sum of the subtest scores was not significantly related to any of the subarachnoid space area–skull area ratios and the ventricular area–skull area ratios in the hemisphere contralateral to the more affected side of the body ($r=0.03$, $P=.96$, and $r=0.01$, $P=.97$, respectively) or in the ipsilateral hemisphere ($r=-0.31$, $P=.49$, and $r=-0.20$, $P=.66$, respectively). The total callosal area–skull area ratio was also correlated with the verbal IQ on the WAIS-R ($r=0.9$, $P<.01$).

When the total callosal area–skull area ratio, the subarachnoid space area–skull area ratio, the ventricular area–skull area ratio, the patient age, and the duration of the clinical course were entered into a stepwise regression analysis, the total callosal area–skull area ratio accounted for a significant proportion of the variances of the mean cortical CMRGlc value and the sum of the WAIS-R subtest scores, with adjusted $R^2=0.66$ and 0.80, respectively; the other variables had not significantly contributed to the magnitude of these $R^2$ values. The callosal area–skull area ratio did not correlate with any of the other MR imaging variables, the patient age, or the duration of the clinical course. Stepwise regression analysis also showed that these variables did not account for a significant proportion of the variances of the callosal area–skull area ratio.

### Table 1. Clinical Data for 8 Patients With Corticobasal Degeneration*

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70</td>
<td>59</td>
<td>49</td>
<td>60</td>
<td>62</td>
<td>72</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Education level, y</td>
<td>8</td>
<td>14</td>
<td>9</td>
<td>14</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Duration, mo</td>
<td>66</td>
<td>48</td>
<td>64</td>
<td>38</td>
<td>42</td>
<td>39</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Asymmetry of signs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>More affected side</td>
<td>R</td>
<td>R</td>
<td>L</td>
<td>L</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>Azekinesia and rigidity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apraxia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cortical sensory loss</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ailen limb</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dystonia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tremor</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Postural instability</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Frontal lobe sign</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysartrhia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Impaired ocular motion†</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>WAIS-R V-IQ</td>
<td>103</td>
<td>83</td>
<td>54</td>
<td>97</td>
<td>NA</td>
<td>111</td>
<td>110</td>
<td>83</td>
</tr>
<tr>
<td>WAIS-R P-IQ</td>
<td>81</td>
<td>85</td>
<td>&lt;40</td>
<td>84</td>
<td>NA</td>
<td>75</td>
<td>92</td>
<td>60</td>
</tr>
<tr>
<td>Sum of 6 scaled scores on WAIS-R‡</td>
<td>49</td>
<td>39</td>
<td>12</td>
<td>42</td>
<td>NA</td>
<td>51</td>
<td>55</td>
<td>27</td>
</tr>
</tbody>
</table>

* WAIS-R indicates Wechsler Adult Intelligence Scale–Revised; V-IQ, verbal IQ; P-IQ, performance IQ; NA, not assessed; plus sign, present; and minus sign, absent.
† Saccadic pursuit or slow eye movement.
‡ Digit Span, Arithmetic, Picture Arrangement, Object Assembly, Block Design, and Digit Symbol.

### Table 2. Mean Area Ratios of the 5 Regions of the Corpus Callosum to the Skull Area in Patients With CBD and Control Subjects*

<table>
<thead>
<tr>
<th>Ratio, %</th>
<th>Anterior</th>
<th>Middle Anterior</th>
<th>Middle Posterior</th>
<th>Posterior</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 36)</td>
<td>1.48 ± 0.15</td>
<td>0.76 ± 0.10</td>
<td>0.65 ± 0.10</td>
<td>1.41 ± 0.19</td>
<td>4.30 ± 0.46</td>
</tr>
<tr>
<td>CBD (n = 8)</td>
<td>0.96 ± 0.24†</td>
<td>0.42 ± 0.14†</td>
<td>0.34 ± 0.14†</td>
<td>1.03 ± 0.22†</td>
<td>2.75 ± 0.59†</td>
</tr>
<tr>
<td>% of Controls</td>
<td>64.6</td>
<td>55.8</td>
<td>52.8</td>
<td>73.2</td>
<td>64.0</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. CBD indicates corticobasal degeneration.
† $P<.001$ vs controls (Student’s t test).

The degree of callosal atrophy was also correlated with the degree of cognitive deterioration (Figure 3). In the patients, the degree of cognitive impairment, as shown by a decrease in the sum of the scaled WAIS-R subtest scores, varied (Table 1). However, the total callosal area–skull area ratio showed a strong correlation with the sum of the subtest scores ($r=0.91$, $P<.005$). The sum of the subtest scores was not significantly related to any of the subarachnoid space area–skull area ratios and the ventricular area–skull area ratios in the hemisphere contralateral to the more affected side of the body ($r=0.03$, $P=.96$, and $r=0.01$, $P=.97$, respectively) or in the ipsilateral hemisphere ($r=-0.31$, $P=.49$, and $r=-0.20$, $P=.66$, respectively). The total callosal area–skull area ratio was also correlated with the verbal IQ on the WAIS-R ($r=0.9$, $P<.01$).

When the total callosal area–skull area ratio, the subarachnoid space area–skull area ratio, the ventricular area–skull area ratio, the patient age, and the duration of the clinical course were entered into a stepwise regression analysis, the total callosal area–skull area ratio accounted for a significant proportion of the variances of the mean cortical CMRGlc value and the sum of the WAIS-R subtest scores, with adjusted $R^2=0.66$ and 0.80, respectively; the other variables had not significantly contributed to the magnitude of these $R^2$ values. The callosal area–skull area ratio did not correlate with any of the other MR imaging variables, the patient age, or the duration of the clinical course. Stepwise regression analysis also showed that these variables did not account for a significant proportion of the variances of the callosal area–skull area ratio.

### Comment

In this study, patients with CBD exhibited atrophy of the corpus callosum, which was associated with cognitive impairment and cerebral cortical hypometabolism. We found...
that the total callosal area–skull area ratio was significantly decreased in patients with CBD, compared with the control subjects. The regional distribution of callosal area in the patients differed from that in the controls, and a prominent decrease in the middle-half area was a pattern of the atrophy of the corpus callosum in CBD that may characterize this disease among other neurodegenerative diseases exhibiting callosal atrophy.10,11,16 The severity of atrophy of the corpus callosum varied but was significantly correlated with a deterioration of cognitive function evaluated with the 6 subtests of the WAIS-R. In addition, atrophy of the corpus callosum was accompanied by decreased mean cortical CMRGlc, with hemispheric asymmetry.

The major cause of atrophy of the corpus callosum may be axonal degeneration arising from damage to cortical neurons.1,2,5 In addition, severe cytoskeletal abnormality in the cerebral white matter might accentuate the degree of callosal atrophy.17 The severity of decrease in callosal size compared with controls was as high as 50% in the middle-half portion, which may indicate severe cerebral cortical involvement in this disease. The middle predominance in the degree of callosal atrophy suggests that the severity of pathological changes in the cerebral cortices has a maximal change in the posterior-frontal and parietal regions, when the topography of the corpus callosum is considered.6 Atrophy of the corpus callosum may reflect both the severity and the pattern of cortical neuronal damage in CBD.

Extensive atrophy of the corpus callosum may relate to global deterioration of cognitive functions in CBD. Patients with CBD may show a specific pattern of neuropsychological deficits associated with deficits in executive functions, likely caused by degeneration of the prefrontal cortex and basal ganglia and praxis disorders, which might be related to premotor and parietal lobe lesions.18 In addition, a subgroup of patients with CBD may have severe apraxia with global cognitive impair-
ment, caused by additional diffuse cortical damage. In this study, the area of the corpus callosum was correlated with the sum of the scaled scores on the WAIS-R subtests sensitive to brain injury. Damage of large-scale networks between cortical regions leading to disconnection, the degree of which may be reflected by atrophy of the corpus callosum, may contribute to the disturbance of complex cortical function in CBD.

Atrophy of the corpus callosum may be the best indicator of cortical dysfunction among the MR imaging findings in CBD. Brain computed tomographic scans or MR images in some patients showed asymmetrical cerebral atrophy affecting mainly the frontal and parietal lobes in the hemisphere opposite the affected limbs, which suggested asymmetrical cortical involvement typical of CBD. In others, however, they showed normal findings or generalized cortical atrophy, which was accompanied by a characteristic asymmetrical decrease of cortical metabolism, when studied with PET. In this study, the degree of cognitive impairment and metabolic decline showed a stronger correlation with the severity of atrophy of the corpus callosum than with the cortical atrophy or ventricular dilatation. Thus, atrophy of the corpus callosum may be a useful finding relating to cognitive impairment accompanied by cortical hypometabolism in CBD.

There may be developmental variation of callosal size predisposing or contributing to the asymmetry of this disease and other alternative causes of decreased callosal size other than atrophy. Thus, longitudinal studies should be done to determine whether progression of callosal atrophy is correlated with cognitive deterioration or metabolic decline. We could not study the control subjects by both PET and MR imaging. The value of our finding would have been greatly enhanced if a lack of correlation between cortical glucose metabolism and callosal size had been found for the normal population. A primary callosal lesion does not irreversibly reduce cerebral cortical glucose metabolism or intellectual function. Thus, the correlation of callosal size with cognitive impairment with cerebral cortical hypometabolism suggests that the pathological changes in the cerebral cortex caused these morphological and functional changes. The decrease in cortical glucose metabolism may have resulted from cortical atrophy through the partial volume effect. However, substantial metabolic changes were detected even in patients with slight cortical atrophy. Thus, the degree of cortical atrophy was not correlated with either cortical glucose metabolism or callosal size. Neuronal loss in the cerebral cortex may not necessarily be reflected by cortical atrophy because of reactive gliosis. However, atrophy of the corpus callosum may reflect more sensitively the severity of cortical neuronal loss because of the vulnerability of cortical layer 3.

In conclusion, atrophy of the corpus callosum, especially in the middle-half portion, is present in CBD, and this atrophy is associated with cognitive impairment and cerebral cortical hypometabolism with hemispheric asymmetry. The severity and extent of cortical involvement may be reflected by atrophy of the corpus callosum, which may characterize this disease among other disorders that manifest akinetic-rigid syndrome that may show only mild cortical abnormality. Interference with the operations of corticocortical connections may be an important factor in the development of cortical dysfunction in CBD.

Accepted for publication October 10, 1997.

We thank Yoshiharu Yonekura, MD, PhD, Fukui Medical School, Fukui, Japan, and the staff of the Department of Radiology and Nuclear Medicine, Faculty of Medicine, Kyoto University, for their support and technical help.

Reprints: Hidenao Fukuyama, MD, PhD, Department of Brain Pathophysiology, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606, Japan (e-mail: fukuyama@kuhp.kyoto-u.ac.jp).

REFERENCES