Correlation Between Antemortem Magnetic Resonance Imaging Findings and Pathologically Confirmed Corticobasal Degeneration

Keith A. Josephs, MST, MD; David F. Tang-Wai, MD, CM; Steven D. Edland, PhD; David S. Knopman, MD; Dennis W. Dickson, MD; Joseph E. Parisi, MD; Ronald C. Petersen, PhD, MD; Clifford R. Jack, Jr, MD; Bradley F. Boeve, MD

Background: Slowly progressive asymmetric parkinsonism and cortical dysfunction clinically characterize corticobasal syndrome (CBS). Various pathologic findings, including corticobasal degeneration (CBD), progressive supranuclear palsy, and frontotemporal degenerations, underlie CBS.

Objective: To determine if regional cerebral cortical and corpus callosum atrophy and subcortical and periventricular white matter (SPWM) signal changes on head magnetic resonance imaging were specific to CBD.

Design: Historical review of autopsy cases.

Setting: Subspecialized behavioral neurology and movement disorder clinics within a neurology department of a tertiary referral center.

Patients: Seventeen patients with CBS who had an autopsy-confirmed diagnosis of CBD or another neurodegenerative disease.

Main Outcome Measures: Regional cerebral cortical atrophy, regional corpus callosum atrophy, and SPWM signal changes.

Results: Similar patterns of regional atrophy and SPWM signal changes were found in the patients with autopsy-proven CBD and in the patients with other neurodegenerative diseases.

Conclusion: Neither cortical nor corpus callosum atrophy nor SPWM signal changes on head magnetic resonance imaging are specific to CBD.

Arch Neurol. 2004;61:1881-1884

Corticobasal degeneration (CBD) is often characterized clinically by progressive asymmetric rigidity and apraxia, with other findings suggesting additional cortical (eg, alien limb phenomena, cortical sensory loss, myoclonus, and mirror movements) and basal ganglia (eg, bradykinesia, dystonia, tremor) dysfunction, and has distinctive histopathologic features.1-3 Antemortem diagnosis of CBD remains imperfect since case reports and case series have revealed pathologic heterogeneity, with progressive supranuclear palsy (PSP), Pick disease, nonspecific neurodegeneration, Creutzfeldt-Jakob disease (CJD), Alzheimer disease (AD), motor neuron disease inclusion dementia, neurofilament inclusion body disease, and CBD.3-6 The term corticobasal syndrome (CBS) has therefore been suggested to describe the clinical characterization of the disorder independent of underlying histopathologic findings.3

Specific magnetic resonance imaging (MRI) findings for each neurodegenerative disease have been sought to improve the antemortem diagnosis. The reported MRI findings associated with CBD include: (1) atrophy of the posterior frontal cortex, superior parietal cortex, and middle portion of the corpus callosum on T1-weighted images, (2) hypointense signal changes in the putamen on T1-weighted images, and (3) hyperintense signal changes in the motor cortex or subcortical white matter on T2-weighted images.7-10 Although these findings may be useful in differentiating CBD patients from healthy patients and patients with idiopathic Parkinson disease, there are no published data on these regional anatomic differences or signal changes on MRI reliably differentiating CBD from other neurodegenerative disorders that produce the CBS. Therefore, we sought to determine if regional cerebral cortical atrophy, regional corpus callosum atrophy, or white matter signal changes were predic-
Table. Demographic Characteristics of the 17 Patients With Corticobasal Syndrome

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at Onset, y</th>
<th>Duration of Illness, y Before MRI, y</th>
<th>Pathologic Diagnosis</th>
<th>Clinically Significant Affected Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Clinical and Pathologic Diagnosis of CBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/F/72</td>
<td>4</td>
<td>1</td>
<td>CBD</td>
</tr>
<tr>
<td>2/M/68</td>
<td>6</td>
<td>2</td>
<td>CBD</td>
</tr>
<tr>
<td>3/F/69</td>
<td>6</td>
<td>4</td>
<td>CBD</td>
</tr>
<tr>
<td>4/M/73</td>
<td>6</td>
<td>4</td>
<td>CBD</td>
</tr>
<tr>
<td>5/F/66</td>
<td>6</td>
<td>2</td>
<td>CBD</td>
</tr>
<tr>
<td>6/M/66</td>
<td>6</td>
<td>4</td>
<td>CBD</td>
</tr>
<tr>
<td>Group 2: Clinical Diagnosis of CBS but Non-CBD Pathologic Features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/M/57</td>
<td>4</td>
<td>2</td>
<td>CJD</td>
</tr>
<tr>
<td>8/M/68</td>
<td>2</td>
<td>1</td>
<td>PSP</td>
</tr>
<tr>
<td>9/M/79</td>
<td>7</td>
<td>1</td>
<td>PSP</td>
</tr>
<tr>
<td>10/M/59</td>
<td>8</td>
<td>3</td>
<td>FTD</td>
</tr>
<tr>
<td>11/M/67</td>
<td>7</td>
<td>4</td>
<td>PSP</td>
</tr>
<tr>
<td>12/M/62</td>
<td>8</td>
<td>5</td>
<td>AD</td>
</tr>
<tr>
<td>13/F/68</td>
<td>3</td>
<td>3</td>
<td>FTD</td>
</tr>
<tr>
<td>14/M/52</td>
<td>8</td>
<td>6</td>
<td>PSP</td>
</tr>
<tr>
<td>15/M/49</td>
<td>5</td>
<td>3</td>
<td>FTD</td>
</tr>
<tr>
<td>16/F/60</td>
<td>5</td>
<td>2</td>
<td>AD</td>
</tr>
<tr>
<td>17/M/69</td>
<td>3</td>
<td>2</td>
<td>CJD</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CBD, corticobasal degeneration; CJD, Creutzfeldt-Jacob disease; FTD, frontotemporal degeneration; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy.

tors of underlying CBD in CBS. These abnormalities were chosen because they are most likely to be used by clinicians who evaluate patients with CBS.

SELECTION OF CASES
The Mayo Clinic Electronic Records Database was used to identify all autopsy cases between January 1, 1988, and December 31, 2001, with the clinical diagnosis of CBS or probable CBD. We identified 40 such cases. Of these, 17 had at least one complete MRI, defined as inclusion of both axial T1- and T2-weighted images and sagittal T1-weighted images, available for review. (Fluid-attenuated inversion recovery images were available only in a few cases.) The historical records of these 17 patients were reviewed by 2 neurologists (K.A.J. and D.F.T-W.) to determine if they all fit recent published criteria for CBS.3 Each case was then placed in 1 of 2 groups. Group 1 consisted of patients with the clinical and pathologic diagnosis of CBS and CBD, respectively, and group 2 consisted of patients with a clinical diagnosis of CBS but a pathologic diagnosis other than CBD.

CLINICAL DIAGNOSIS
The clinical diagnosis of CBS was based on the presence of progressive asymmetric rigidity and apraxia, as well as other findings that reflect cortical (eg, alien limb phenomenon, cortical sensory loss, myoclonus) and extrapyramidal dysfunction (eg, tremor, dystonia).3 All cases also fulfilled other published criteria for the clinical diagnosis of CBD.11,12

PATHOLOGIC DIAGNOSES
The pathologic diagnoses of CBD and other neurodegenerative and prion disorders were made by 1 of 2 neuropathologists (D.W.D. or J.E.P.) based on recent consensus diagnostic criteria.2,13

MRI REVIEW
Anatomic regions of interest (ROIs) in both hemispheres for each of the 17 patients were outlined on the MRIs in a standardized manner using the template method of Damasio and Damasio.14 Note that herein ROI is not used in the traditional sense (ie, segmentation of the borders of an anatomic structure for purposes of quantitation) but instead as an anatomic guide for raters who perform categorical lobar atrophy scoring. The cortical ROI included the: (1) anterior and posterior frontal lobes, (2) anterior, mesial, and lateral temporal lobes, (3) superior and inferior parietal lobes, and (4) occipital lobes. The ROI of the corpus callosum was divided into 3 sections: anterior, middle, and posterior. Blinded to the clinical and pathologic diagnoses, 1 neuroradiologist (C.R.J.) and 3 behavioral neurologists (B.F.B., R.C.P., D.S.K.) rated the presence and severity of atrophy for each ROI and the presence or absence of increased T2-weighted signal changes in subcortical and periventricular white matter (SPWM). Each ROI was rated as no to minimal atrophy (0-1) or moderate to severe atrophy (2-3). The mean value of the 4 raters for each ROI was calculated.

CLINICOPATHOLOGIC IMAGING COMPILATION
For each case, the clinical diagnosis was matched to the corresponding pathologic diagnosis. The MRI findings were rated as either contralateral or ipsilateral to the main affected cerebral hemisphere determined from the main affected limb.

STATISTICAL ANALYSES
The Spearman rank correlation coefficient was used to assess the interrater reliability of atrophy measurements and white matter scores. The Wilcoxon rank sum test was used to determine any significant differences in cortical atrophy at each ROI as measured by the mean of all 4 reviewers' scores and by the individual reviewer scores.

The demographic data for all 17 patients are listed in the Table. Representative MRIs scans from groups 1 and 2 are shown in Figure 1. All 17 patients fit clinical diagnostic criteria for CBS.3 There were 6 patients (3 men and 3 women) in group 1 and 11 patients (9 men and 2 women) in group 2. The mean ± SD age at onset of symptoms and duration of illness for each group, respectively, were 69.0 ± 3.0 years and 5.7 ± 0.8 years (group 1) and 62.7 ± 8.6 years and 5.5 ± 2.3 years (group 2). The right side was the predominant affected side in 2 patients in group 1 and in 6 patients in group 2.

Ratings of the same ROI by different raters were significantly correlated for most pairwise comparisons (0.91 ± r ± 0.36, P = .04), suggesting reasonable reliability. The only exception was for 2 raters’ scores of the anterior temporal and superior parietal ROI. The duration from onset of illness to MRI between the 2 groups was not significantly different. The topographic distribution and the average degree of atrophy among the 4 reviewers for each group are shown in Figure 2. Posterior frontal, superior...
parietal, and middle corpus callosum atrophy were present in both groups. The Wilcoxon rank sum test showed no significant difference among each of the cortical ROIs outlined for the 2 groups for all reviewers and individual reviewers, and thus there was no distinctive pattern of regional atrophy that distinguished one group from the other. Interestingly, there was minimal temporal lobe atrophy in patients with a pathologic diagnosis of PSP or CJD. The SPWM signal changes were found in 5 of 11 patients from group 2 and in 2 patients from group 1.

The CJD patients had unusually long durations of their illness: 4 years for patient 7 and 3 years for patient 17. Both patients underwent MRI before fluid-attenuated inversion recovery and diffusion-weighted images were developed. Thus, no imaging features during life suggested a prion disorder.

Like all other patients in this series, the 2 AD patients exhibited typical features of CBS1 (Figure 1B, group 2). Neither had functional or clinical evidence of memory impairment. Neither patient underwent imaging sequences that allowed hippocampal volume analyses.

**COMMENT**

The results of this study revealed the presence of atrophy of the posterior frontal, superior parietal, and middle corpus callosum in both groups. The distribution of atrophy did not differentiate groups with or without a pathologic diagnosis of CBD. Our findings are similar to those reported by Schrag and colleagues.15 The SPWM signal changes also were neither sensitive nor specific for CBD. The poor positive predictive value for underlying CBD in those with the clinical diagnosis of CBS supports the contention that antemortem diagnosis of CBD remains challenging and cannot be made with confidence based on the clinical features alone.3,4 In our series, only 35% of patients with the clinical diagnosis of CBS had underlying CBD. Our findings are not surprising, since the clinical features in CBS reflect parietofrontal and transcallosal dysfunction, and this pattern of atrophy would be expected in CBS regardless of histopathologic features. Hence, the pattern of MRI atrophy reflects the clinical syndrome but not the underlying pathologic findings.

The nosonomy of CBS and CBD and the relationship to frontotemporal dementia, frontotemporal degeneration, and PSP continue to evolve. Corticobasal syndrome refers to the constellation of clinical features that reflect parietofrontal cortical dysfunction; degeneration of the basal ganglia and substantia nigra is not necessary to produce the syndrome.3 Frontotemporal dementia refers to the constellation of clinical features that reflect frontotemporal cortical dysfunction,17 whereas frontotemporal degeneration refers to pathologic diagnosis.18 The pathologic entities of CBD, frontotemporal degeneration, and PSP can underlie the syndromes of CBS and frontotemporal dementia, as well as primary progressive aphasia.2 The Pick complex nomenclature has been suggested,19 which encompasses several of these focal cortical degeneration syndromes and neurodegenerative disorders, although this term was not widely endorsed by members

![Figure 1](http://archneur.jamanetwork.com/)  
*Figure 1.* Axial fluid-attenuated inversion recovery head magnetic resonance image (MRI) reveals asymmetric (right greater than left) cortical atrophy and mild to moderate right frontal subcortical and periventricular white matter signal changes in patient 1 with corticobasal degeneration from group 1 (A), whereas axial T1-weighted head MRI reveals asymmetric (right greater than left) frontoparietal atrophy in patient 16 with Alzheimer disease from group 2 (B).

![Figure 2](http://archneur.jamanetwork.com/)  
*Figure 2.* Topographic distribution of the average atrophy. In these 8 cortical regions of interest, no significant difference in the degree of atrophy between groups 1 and 2 were found. AF indicates anterior frontal; PF, posterior frontal; AT, anterior temporal; MT, mesial temporal; LT, lateral temporal; SP, superior parietal; IP, inferior parietal; O, occipital.

©2004 American Medical Association. All rights reserved.
of a recent symposium. The concept, however, is important, because it suggests a grouping of disorders that are somewhat similar yet clearly different from AD. With the exception of rare cases, as in patients 12 and 16, differentiating these cases from AD should not be difficult, because the pattern of atrophy in AD differs significantly, primarily affecting the hippocampi.

We also report the incidental finding of minimal to absent temporal lobe atrophy in all patients with the pathologic diagnosis of PSP or CJD. Although we had only a few cases, this is an interesting observation, and future analyses may prove it to be useful in differentiating PSP or CJD from CBD in patients with CBS. Diffusion-weighted imaging was not completed in either CJD patient but may have been useful to rule out CBD if typical findings of CJD were present, including hyperintensity in the cortical ribbon and basal ganglia.

This study has a few limitations that warrant discussion. The MRI changes were not correlated with pathologic findings, since only half of the brain was available for analysis (the other half was frozen post mortem). Although a control group was not used in this study, the purpose of this study was not to differentiate CBD from healthy controls or patients with PD but rather from other diseases that can cause CBS. Neither the presence of regional atrophy nor SPWM signal changes differentiated CBD from other neurodegenerative disorders; however, we did not specifically address other subcortical MRI abnormalities, including striatal signal changes and brainstem and hippocampal atrophy, which may be more helpful predictors. Furthermore, the small sample sizes do not allow us to perform a formal interrater reliability analysis using k statistics or to rule out the possibility of small between-group differences. However, because the goal of the analysis was to aid in clinical diagnosis, we were not interested in subtle between-group distinctions.

Accepted for Publication: April 29, 2004.

Correspondence: Keith A. Josephs, MST, MD, Department of Neurology, Divisions of Behavioral Neurology and Movement Disorders, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (josephs.keith@mayo.edu).

Author Contributions: Study concept and design: Josephs, Tang-Wai, Jack, Boeve. Acquisition of data: Tang-Wai, Knopman, Dickson, Parisi, Boeve. Analysis and interpretation of data: Tang-Wai, Edland, Petersen, Boeve. Drafting of the manuscript: Josephs, Edland. Critical revision of the manuscript for important intellectual content: Tang-Wai, Knopman, Dickson, Parisi, Petersen, Jack, Boeve. Statistical analysis: Edland, Jack. Obtained funding: Petersen, Dickson, Parisi, Boeve. Study supervision: Knopman, Jack, Boeve.

Funding/Support: This study was supported by grants P50 AG 16574 and U01 AG 06786 from the National Institute on Aging, Bethesda, Md, and by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program of the Mayo Foundation.

Previous Presentation: This study was presented and highlighted at the American Academy of Neurology Annual Meeting; April 13, 2002; Denver, Colo.

Acknowledgment: We thank Kris Johnson, RN, for locating many of the MRIs and Stephen Weigand, MS, for advice on statistical methods and study design.

REFERENCES