Multimodal imaging evidence of pathology-mediated disease distribution in corticobasal syndrome

Corey T. McMillan, PhD
Clara Boyd, MD
Rachel G. Gross, MD
Jessica Weinstein, MD
Kim Firn, MS
Jon B. Toledo, MD, PhD
Katya Rascovsky, PhD
Leslie Shaw, PhD
David A. Wolk, MD
David J. Irwin, MD
Edward B. Lee, MD, PhD
John Q. Trojanowski,
MD
Murray Grossman, MD,
EdD

Correspondence to
Dr. McMillan:
mcmillan@mail.med.upenn.edu

ABSTRACT

Objective: To use multimodal neuroimaging to evaluate the influence of heterogeneous underlying pathology in corticobasal syndrome (CBS) on the neuroanatomical distribution of disease.

Methods: We performed a retrospective evaluation of 35 patients with CBS with T1-weighted MRI, diffusion tensor imaging, and neuropathologic, genetic, or CSF evidence of underlying pathology. Patients were assigned to 2 groups: those with evidence of Alzheimer pathology (CBS-AD) and those without Alzheimer pathology (CBS-non-AD). Group comparisons of CBS-AD and CBS-non-AD assessed clinical features, gray matter (GM) cortical thickness, and white matter (WM) fractional anisotropy.

Results: CBS-AD was found in 34% (n = 12) and CBS-non-AD in 66% (n = 23) of CBS patients. Clinical evaluations revealed that CBS-non-AD had a higher frequency of asymmetric rigidity compared to CBS-AD, but groups otherwise did not differ in dementia severity, impairments in cognition, or rates of extrapyramidal symptoms. We found frontoparietal GM and WM disease in each group compared to healthy, demographically comparable controls, as well as multimodal neuroimaging evidence of a double dissociation: CBS-non-AD had WM disease in the corpus callosum, cortico-spinal tract, and superior longitudinal fasciculus relative to CBS-AD, and CBS-AD had reduced temporoparietal GM relative to CBS-non-AD, including the precuneus and posterior cingulate.

Conclusions: Patients with CBS have a pathology-mediated dissociation of GM and WM disease. Multimodality neuroimaging may be useful for improving in vivo pathologic diagnosis of CBS.

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GLOSSARY

AD = Alzheimer disease; **CBS** = corticobasal syndrome; **CDR** = clinical dementia rating; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FTLD** = frontotemporal lobar degeneration; **GM** = gray matter; **t-tau** = total tau.

Corticobasal syndrome (CBS) is a neurodegenerative condition characterized by lateralized extrapyramidal features and cortically mediated cognitive dysfunction.¹ The underlying pathology of CBS is heterogeneous, and clinical features appear to be insufficient to identify an individual's histopathologic abnormality during life.^{2,3} The most common neuropathologic causes of CBS include corticobasal degeneration, a 4-repeat form of tau pathology associated with frontotemporal lobar degeneration (FTLD),⁴ and Alzheimer disease (AD).^{2,5,6}

Multimodal neuroimaging studies suggest that AD and FTLD can be dissociated on the basis of gray matter (GM) and white matter (WM) neuroimaging.^{7,8} Specifically, GM atrophy was evident in both AD and FTLD in T1-weighted MRI studies, but diffusion tensor imaging (DTI) revealed more WM disease in FTLD than in AD. Additional neuroimaging evidence suggests that tau pathology, the most common form of underlying pathology in CBS, is associated with substantial WM imaging changes⁹ and that these findings converge with neuropathologic evidence of WM disease burden in 4-repeat tauopathy.^{9,10} However, prior evidence of greater WM pathology in FTLD disorders has been based on clinically heterogeneous study samples; therefore, it is not clear whether a dissociation of GM and WM disease is

Supplemental data
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From the Department of Neurology (C.T.M., C.B., R.G.G., J.W., K.F., K.R., D.A.W., D.J.I., M.G.) and Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine (J.B.T., L.S., D.J.I., E.B.L., J.Q.T.), Perelman School of Medicine, University of Pennsylvania, Philadelphia.

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related to distinct sources of underlying pathology or confounded by mixed clinical phenotypes.

The goal of the present study was to evaluate whether distinct sources of AD or FTLT pathology mediate the clinical presentation and disease distribution observed in CBS. Specifically, we hypothesized a double dissociation in which CBS due to AD (CBS-AD) would be associated with substantial GM disease and relatively preserved WM and CBS likely due to FTLT (CBS-non-AD) would be associated with more substantial WM disease and relatively preserved GM structure.

METHODS Participants. We performed a retrospective evaluation of 35 patients diagnosed with CBS by a board-certified neurologist in the Penn Frontotemporal Degeneration Center or movement disorders clinics at the University of Pennsylvania. All patients additionally met a diagnosis of possible or probable CBS with the use of published criteria,¹ as summarized in table 1. Inclusion criteria for patients were a research-quality T1-weighted MRI and DTI scan, biomarker evidence of underlying neuropathology (CSF, genetics, or postmortem neuropathologic examination), and adequately detailed clinical notes to obtain a clinical dementia rating (CDR) scale and support confirmation of a CBS diagnosis in a retrospective chart review and assessment of clinical signs and symptoms associated with CBS. CDR and clinical assessments were evaluated at the clinical visit closest to MRI (mean 0.9 months, SD 2.9 months). We excluded patients taking neuroleptic medications other than quetiapine to avoid the possibility of a drug-induced extrapyramidal syndrome. We also excluded patients with evidence of vascular disease, equivalent to Fazekas criteria >1,¹¹ from visual inspection of a T2-weighted image.

We additionally recruited 79 community-dwelling and demographically comparable healthy controls who were screened

to have a Mini-Mental Status Examination score >27 (of 30) and self-reported a negative neurologic or psychiatric history. Three-way Kruskal-Wallis tests did not identify a statistical difference between the healthy control, CBS-non-AD, and CBS-AD groups for age ($\chi^2 = 3.428$, $p = 0.180$) and education ($\chi^2 = 4.094$, $p = 0.129$), and χ^2 analysis revealed no differences for sex across groups ($\chi^2 = 0.79$, $p = 0.68$). Table 1 provides a summary of control and patient demographic features.

Standard protocol approvals, registrations, and patient consents. All patients with CBS and healthy controls participated in a written informed consent procedure approved by the University of Pennsylvania–convened Institutional Review Board.

Neuropathologic subgrouping procedures. For autopsied patients ($n = 5$), neuropathologic assessment was performed on standard tissue regions^{12,13} by an experienced neuropathologist (J.Q.T., E.B.L.) using previously described immunohistochemical methods¹² and diagnostic criteria.^{13,14}

Nonautopsied patients were classified as CBS-non-AD and CBS-AD on the basis of either genetic status or CSF analyses. Patients with a high family history¹⁵ were genotyped for mutations in *MAPT*, *GRN*, and *C9orf72* expansions, as previously reported.¹⁶ CSF was evaluated with a pathology-validated total tau (t-tau): $A\beta_{1-42}$ ratio cutoff of 0.34 with >90% accuracy.¹⁷ Briefly, CSF was obtained for all patients and analyzed in duplicate with either a sandwich ELISA or Luminex t-tau and $A\beta_{1-42}$ levels. We used a t-tau: $A\beta_{1-42}$ cutoff that has been previously demonstrated to have >90% sensitivity and specificity for discriminating between AD and non-AD,¹⁷ where t-tau: $A\beta_{1-42} \geq 0.34$ was associated with AD pathology and t-tau: $A\beta_{1-42} < 0.34$ was associated with non-AD pathology.

Neuroimaging acquisition and analysis. All participants underwent a structural T1-weighted magnetization-prepared rapid-acquisition gradient echoMRI acquired from a SIEMENS 3.0T Trio scanner with an 8-channel coil using the following parameters: repetition time = 1,620 milliseconds; echo time = 3 milliseconds; slice thickness = 1.0 mm; flip angle = 15° ; matrix = 192×256 , and in-plane resolution = 0.9×0.9 mm. Diffusion-weighted images were acquired in a single-shot, spin-echo, 30-direction diffusion-weighted echo planar imaging sequence

Table 1 Summary of demographic and clinical profiles of healthy controls and patients with corticobasal syndrome with Alzheimer disease (CBS-AD) and non-Alzheimer disease (CBS-non-AD) forms of pathology

Measure	Healthy controls	CBS-non-AD	CBS-AD	p Value
Male/female, n	79 (33/46)	23 (8/15)	12 (6/6)	0.675 ^a
Mean (SD) age at MRI, y	64.80 (7.54)	66.65 (11.38)	62.92 (8.45)	0.180 ^b
Mean (SD) education, y	15.95 (2.41)	15.13 (2.05)	14.83 (3.38)	0.129 ^b
Mean (SD) disease duration, y	...	2.83 (1.37)	4.33 (2.74)	0.261
Possible CBS/probable CBS, n	...	6/17	4/8	0.955
Median (IQR) CDR global	...	0.50 (0.0–0.5)	0.50 (0.5–0.5)	0.495
Median (IQR) CDR sum of boxes	...	1.5 (0.5–3.9)	1.75 (1.0–3.6)	0.717
Median (IQR) CDR behavior supplement	...	0.00 (0.0–0.0)	0.00 (0.0–0.0)	0.541
Median (IQR) CDR language supplement	...	0.50 (0.0–1.0)	0.75 (0.0–1.3)	0.476
Median (IQR) CDR sum of boxes + supplement	...	2.25 (0.8–4.9)	2.50 (1.8–3.8)	0.833

Abbreviations: CDR = clinical dementia rating; IQR = interquartile range.

Unless otherwise noted, p values reflect χ^2 comparisons between CBS-non-AD and CBS-AD.

^aThe p value reflects χ^2 test comparisons among 3 groups (healthy controls, CBS-non-AD, and CBS-AD).

^bThe p value reflects Kruskal-Wallis test among 3 groups (healthy controls, CBS-non-AD, and CBS-AD).

(field of view = 245 mm; matrix size = 128 × 128; number of slices = 57; voxel size = 2.2 mm isotropic; repetition time = 6,700 milliseconds; echo time = 85 milliseconds; fat saturation). In total, 34 volumes were acquired per patient, 4 without diffusion weighting ($b = 0$ seconds/mm²) and 30 with diffusion weighting ($b = 1,000$ seconds/mm²) along 30 noncollinear directions. All T1 and DTI image preprocessing was performed with Advanced Normalization Tools, which provides a state-of-the-art pipeline as previously reported¹⁸ and described in detail in appendix e-1 at Neurology.org. We report voxelwise analyses of cortical thickness for GM and fractional anisotropy (FA) for WM.

Statistical procedures. Inspection of demographic data revealed nonnormal distributions; therefore, continuous demographic features were assessed with nonparametric Kruskal-Wallis tests, and categorical features were assessed with χ^2 tests for comparisons of 3 groups (healthy controls, CBS–non-AD, and CBS-AD). Patient group comparisons of the presence or absence of clinical features were performed with χ^2 tests (<https://cran.r-project.org/>).

Cortical thickness and DTI analyses were performed in SPM8 with the 2-sample t -test module. To constrain comparisons to regions of likely GM for the cortical thickness analyses and regions of likely WM for the FA analyses, we generated an explicit mask using an average of all patient and control data that was thresholded to include a minimum mean of GM (>0.4 -mm thickness) and WM (>0.3 FA). The inclusion of an overrepresentation of controls relative to patients in the generation of the explicit masks greatly reduces the chances that a single patient group could bias the selection of regions included in each mask. Comparisons of CBS groups to healthy controls used a $p < 0.05$ (family-wise error corrected) height threshold and a 100 adjacent voxel extent. For direct comparisons of CBS–non-AD and CBS-AD, we report a $q < 0.05$ (false discovery rate corrected) threshold and a minimum of 100 adjacent voxels.

RESULTS Neuropathologic subgroups of CBS. Postmortem neuropathologic assessments were available for 5 patients: 2 individuals had a primary neuropathologic

diagnosis of AD, 2 individuals had underlying PSP pathology, and 1 patient had FTLT with TDP-43 inclusions. Genetic analyses revealed 1 individual with a pathogenic *MAPT* mutation (p.301S) and 2 individuals with a pathogenic *GRN* mutation (c.813_816delCACT and p.418X). For the remaining cases, a CSF τ -tau:A β_{1-42} ratio¹⁷ was used was used to group 10 cases as CBS-AD (≥ 0.34) and 17 cases as CBS–non-AD (<0.34). In summary, we identified at total of 12 individuals (34.29%) who had evidence of CBS-AD (2 neuropathologic diagnoses and 10 CSF) and 23 individuals (65.71%) who had evidence of CBS–non-AD (3 neuropathologic diagnoses, 3 genetic mutations, and 17 CSF).

Clinical results. CBS neuropathologic subgroups did not differ in demographic features or CDR at the time of MRI (table 1). We also assessed whether there was an association between neuropathologic subgroup and possible vs probable CBS clinical criteria, and this analysis revealed an equivocal distribution of diagnostic category across CBS-AD and CBS–non-AD (table 1).

A retrospective assessment of clinical signs and symptoms revealed that CBS-AD and CBS non-AD differed only with a higher frequency of asymmetric rigidity for CBS–non-AD relative to CBS-AD ($\chi^2 = 4.624$; $p = 0.032$). As summarized in figure 1, the remainder of the evaluated clinical features did not differ across neuropathologic subgroups, including apraxia ($\chi^2 = 0.972$; $p = 0.789$), cortical sensory loss ($\chi^2 = 0.000$; $p = 1.000$), myoclonus ($\chi^2 = 1.993$; $p = 0.158$), dystonia ($\chi^2 = 0.004$; $p = 0.948$), visuospatial impairments ($\chi^2 = 2.081$; $p = 0.149$), executive dysfunction

Figure 1 Clinical features of corticobasal syndrome patients with Alzheimer disease or non-Alzheimer disease

($\chi^2 = 0.042$; $p = 0.837$), naming difficulty ($\chi^2 = 2.081$; $p = 0.149$), and episodic memory impairments ($\chi^2 = 3.302$; $p = 0.069$).

Cortical thickness. Relative to healthy controls, CBS–non-AD patients have reduced cortical thickness in bilateral inferior parietal and frontal cortical regions, including left primary motor and right supplementary motor cortices. In contrast, CBS-AD patients have more extensive reductions in cortical thickness relative to healthy controls in the right inferior parietal cortex extending to the bilateral fusiform and temporal regions, along with left primary motor cortex, left dorsomedial prefrontal cortex, and bilateral ventral striatum. Table e-1 and figure e-1 provide a summary of cortical thickness results for each CBS group relative to healthy controls.

Direct comparisons of CBS groups revealed reduced cortical thickness in CBS-AD relative to CBS–non-AD in the left parietal cortex, including the inferior parietal, posterior cingulate, and angular gyrus regions that extend to include the inferomedial temporal cortex, along with the right fusiform gyrus (table 2, figure 2). CBS–non-AD did not have any cortical thickness reductions relative to CBS-AD.

WM FA. A comparison of CBS–non-AD relative to healthy controls revealed extensive bilateral reductions of FA in the superior longitudinal fasciculus, corpus callosum, inferior longitudinal fasciculus, inferior frontal-occipital fasciculus, and anterior thalamic radiations, as well as lateralized reductions in the left cingulum, right middle cerebellar peduncle, and left

Table 2 Regions of reduced gray matter (GM) density and reduced fractional anisotropy in white matter (WM) for direct comparisons of corticobasal syndrome with Alzheimer disease (CBS-AD) and non-Alzheimer disease (CBS–non-AD)

Neuroanatomic region (Brodmann area)	L/R	Peak voxel MNI coordinates			q Value of peak voxel	Cluster size (voxels), n
		x	y	z		
GM cortical thickness: CBS-AD < CBS-non-AD						
Inferior parietal (40)	L	−40	−42	36	0.001	267
Posterior cingulate (31), angular gyrus (39)	L	−28	−68	24	0.008	240
Posterior cingulate (31)	L	−12	−50	32	0.001	773
Posterior cingulate (23/31)	L	−12	−60	8	0.010	126
Inferomedial temporal gyrus (19)	L	−28	−60	−8	0.001	3,632
Fusiform gyrus (37)	R	28	−54	−16	0.005	246
WM fractional anisotropy: CBS-non-AD < CBS-AD						
Superior longitudinal fasciculus	L	−46	−6	49	0.012	112
Superior longitudinal fasciculus	L	−50	−2	15	0.010	597
Corpus callosum	...	−6	−3	24	0.003	4,460
Corpus callosum	...	−5	26	11	0.026	114
Corpus callosum	L	−21	−42	24	0.006	347
Corpus callosum	L	−11	11	59	0.001	1,068
Corpus callosum	L	−14	32	11	0.015	205
Corpus callosum	R	10	−1	65	0.003	237
Corpus callosum	R	14	−1	45	0.009	109
Corpus callosum	R	10	12	54	0.009	555
Corticospinal tract	...	7	−17	67	0.003	246
Corticospinal tract	L	−27	−27	23	0.001	1,124
Corticospinal tract	L	−19	−19	69	0.007	196
Corticospinal tract	L	−25	−12	13	0.013	132
Corticospinal tract	L	−20	−10	−9	0.006	174
Corticospinal tract	R	31	−29	62	0.007	357
Anterior thalamic radiation	L	−15	−3	8	0.008	203
Anterior thalamic radiation	L	−35	12	20	0.013	135

Abbreviation: MNI = Montreal Neurological Institute.

All results reported at $q < 0.05$ (false discovery rate corrected) with >100 adjacent voxel extent.

Figure 2 Multimodal neuroimaging of corticobasal syndrome patients with Alzheimer disease (CBS-AD) or without Alzheimer disease (CBS-non-AD)

(A) reduced cortical thickness for CBS-AD relative to CBS-non-AD; (B) reduced white matter fractional anisotropy for CBS-non-AD relative to CBS-AD (yellow regions) overlaid on red/green/blue images illustrating average diffusion direction (red = left/right; green = anterior/posterior; blue = superior/inferior).

corticospinal tract. A comparison of CBS-AD with healthy controls revealed reduced FA in the bilateral inferior longitudinal fasciculus, corpus callosum, and cingulum, and lateralized reductions in the left superior longitudinal fasciculus and WM of the right globus pallidus and ventral striatum. Figure e-1 and table e-1 summarize FA reductions for each CBS group relative to healthy controls.

Direct comparisons of CBS groups revealed reduced FA in CBS-non-AD relative to CBS-AD in the superior longitudinal fasciculus, corpus callosum, bilateral corticospinal tract, and left anterior thalamic radiations (table 2, figure 2). CBS-AD, however, did not have any FA reductions relative to CBS-non-AD.

DISCUSSION Our observations establish proof-of-concept evidence that pathology can mediate neurodegenerative disease distribution by demonstrating that distinct neuroanatomical correlates can be associated with a common clinical syndrome. This has important implications for identifying early patterns of disease for neuroprotective clinical trials and for informing longitudinal analyses that aim to monitor disease spread in the context of a clinical trial. The

following paragraphs address the biological and clinical relevance of the observed GM-WM double dissociation in CBS.

The observed dissociation of GM and WM in pathologic subgroups of CBS is consistent with recent work in clinically heterogeneous samples. These studies suggested that on average there is reduced FA in the anterior corpus callosum of FTL and reduced GM in the precuneus and posterior cingulate of AD.^{7,8} While the neuroanatomic distribution of disease that contributed to classification in prior studies could be confounded by the clinical heterogeneity of the samples, the current study observed similar regions contributing to pathologic heterogeneity in a single clinical syndrome. Specifically, anterior corpus callosum WM and precuneus and posterior cingulate GM appear also to differentiate CBS-non-AD and CBS-AD. Additional regions that differed between groups included temporal cortex GM and the superior longitudinal fasciculus of WM, which may provide additional specificity for differentiating pathologic forms of CBS that may not have otherwise been identified in clinically heterogeneous samples.

The loci of GM and WM disease observed in the current study are consistent with prior neuropathologic

and neuroimaging reports of AD and FTLN pathology. Prior histopathologic studies have demonstrated extensive WM disease such as astrocytic plaques in CBS–non-AD, while CBS-AD has extensive GM disease,⁴ consistent with our observation of reduced WM integrity in CBS–non-AD. We observed predominantly reduced cortical thickness of temporal cortex in CBS-AD, consistent with a neuroimaging report demonstrating high sensitivity and specificity for PET-amyloid studies of CBS patients categorized as temporal predominant rather than frontal predominant.¹⁹ Our observation of more posterior GM involvement in CBS-AD relative to CBS–non-AD is consistent with similar comparisons of GM imaging,^{2,20} although these prior studies did not assess diffusion measures of WM integrity. Our findings also converge with 2 studies suggesting that reduced WM integrity in the corpus callosum is associated with CBS²¹ and is sensitive and specific for detecting FTLN relative to AD pathology.^{7,8} In one prior neuroimaging report of autopsy-confirmed corticobasal degeneration, GM disease was seen in posterior and superior frontal, insula, and supplementary motor regions, and WM disease was seen in the corpus callosum and external capsule.²² While this study used both GM and WM imaging, this work differs from ours by assessing volumetric measures of WM rather than DTI. In the current study, moreover, we included a user-independent whole-brain analysis of pathologically defined CBS patients. This form of analysis requires minimal a priori assumptions and is similar to a traditional voxel-based morphometry analysis of GM.

The observed loci in the current study also potentially provide insight into sources of diagnostic error in CBS. For example, CBS-AD had reduced GM in the ventral striatum and reduced FA of the WM near the globus pallidus. These regions contribute to the extrapyramidal motor system and therefore may contribute to the parkinsonian signs and symptoms that lead a clinician to diagnose a patient as having CBS or likely corticobasal degeneration pathology. Pathologic staging studies of AD suggest that these regions are affected by tau, although not until later stages (Braak stage IV–VI) of AD pathology.²³ Thus, our observation of striatal involvement in patients with relatively mild (median CDR = 0.5) CBS suggests that striatal regions may be involved at an earlier stage for CBS. Thus, while typical AD is widely assumed to have a stereotypic pattern of pathologic spread,²³ CBS-AD highlights the possibility of distinct patterns of pathologic spread associated with atypical forms of AD. Another possibility is that CBS-AD may additionally be accompanied by comorbid sources of other pathologies such as Lewy body disease, but in vivo biomarkers of α -synuclein are lacking to confirm this possibility. In a small autopsy cases series, approximately half of CBS-AD patients had co-occurring Lewy body pathology, while

CBS–non-AD patients had no evidence of Lewy body pathology.²⁰ Although our CSF criteria are highly sensitive and specific for discriminating between AD and non-AD pathologies,¹⁷ future studies with pathology-confirmed samples are necessary to evaluate the potential influence of comorbid AD and Lewy body pathology contributing to atypical AD syndromes such as CBS.²⁰

In addition to regions hypothesized to affect clinical motor function, we observed regions of overlap in CBS-AD and CBS–non-AD cortical GM regions that may lead to similar forms of cognitive dysfunction. Primarily, the current study and others^{2,19} suggest that both groups have parietal cortex disease in common. This locus of disease may contribute to cognitive dysfunction in CBS, including impairments in number knowledge^{24–27} and linguistic discourse²⁸ that have been associated with parietal disease. Notably, while episodic memory was marginally more common in CBS-AD relative to CBS–non-AD, it was observed in only $\approx 30\%$ of patients, suggesting that memory may not provide a salient biomarker for this form of atypical AD.

Several caveats should be kept in mind when considering our study. CBS is a relatively uncommon syndrome, and we further subdivided our cohort into 2 groups based on each individual's source of underlying pathology, resulting in relatively small sample sizes. Future work in a larger, and ideally multicenter, cohort of CBS patients is needed to confirm our observations and to perform classification of an individual's source of disease that is translatable to a clinical setting. A related consideration is the extent to which the methodology used in our laboratory is generalizable to heterogeneous sources of data and software from other laboratories. Importantly, our image analysis pipeline is shared in an open-source framework to encourage reproducibility, and there are data acquisition efforts to harmonize image acquisition across frontotemporal dementia centers in an attempt to facilitate cross-laboratory validation. It will additionally be important to consider how alternative imaging features such as pattern-based analysis²⁹ compare to our currently implemented voxelwise analysis method.

An additional caveat relates to our use of pathologically validated CSF markers to serve as a surrogate for autopsy observations, and additional work is needed to confirm our findings with direct neuropathologic examination at autopsy. Some cases of CBS associated with underlying FTLN-TDP pathology have been reported,² and the current cohort included a few cases with either FTLN-TDP pathology or *GRN* mutations associated with TDP-43 pathology. While our use of t-tau:A β _{1–42} reliably discriminates between AD and non-AD, it does not discriminate between potential sources of non-AD pathology, including tau or TDP-43 histopathologic abnormalities. Therefore, it

is possible that some CBS–non-AD patients have FTLTDP rather than FTLT-tau pathology, although these cases are less common. Future studies that include autopsy confirmation rather than CSF surrogates of pathology are required to determine whether neuroimaging can help identify specific markers of 4-repeat tauopathy due to corticobasal degeneration that differ from other FTLT forms of CBS such as FTLT-TDP. However, our observation of a small number of confirmed CBS-FTLT pathology cases limits the ability to perform such an assessment of specificity in the current study. Critically, one of the loci that contributed to the discrimination between CBS-AD and CBS–non-AD in the current study was the superior longitudinal fasciculus, which has previously been identified in neuroimaging and neuropathologic analyses as a sensitive and specific region for FTLT-tau relative to FTLT-TDP pathology.⁹

A further caveat to consider is that, although we observed a difference in asymmetric rigidity between CBS-AD and CBS–non-AD, our evaluation of clinical heterogeneity across these pathologic subgroups was constrained to a retrospective chart review. It is possible that prospective assessments of neuropsychological tests and motor evaluations may yield a deeper endophenotype of CBS that can be used to screen individuals for likely forms of underlying pathology.³⁰ Future studies are necessary in an independent cohort to evaluate the sensitivity and specificity of asymmetric rigidity, along with our observed dissociation between neuroimaging features, for improving the diagnosis of underlying pathology in CBS.

With these caveats in mind, this multimodality imaging study demonstrated distinct patterns of GM and WM disease in phenotypically similar patients with CBS due to either AD or non-AD forms of pathology. The ability to predict pathology in vivo in clinically similar patients is essential as treatments targeted at the underlying pathologic process become available. Our findings suggest that multimodality neuroimaging may provide a diagnostic tool to improve the accuracy of determining the pathologic source of an individual's CBS, and this approach may help guide patient selection for treatment trials.

AUTHOR CONTRIBUTIONS

C.T.M., C.B., R.G.G., J.W., K.F., J.B.T., K.R., L.S., D.A.W., D.J.I., E.B.L., J.Q.T., and M.G. drafted and revised the manuscript for content. C.T.M., C.B., R.G.G., J.B.T., D.J.I., and M.G. provided study concept and design. C.T.M., C.B., R.G.G., J.W., K.F., K.R., L.S., D.J.I., E.B.L., J.Q.T., and M.G. performed the analysis and interpretation of the data. C.T.M. and K.F. performed statistical analysis. C.T.M., J.Q.T., and M.G. obtained funding.

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DISCLOSURE

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