Imaging correlates of pathology in corticobasal syndrome

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ABSTRACT

Background: Corticobasal syndrome (CBS) can be associated with different underlying pathologies that are difficult to predict based on clinical presentation. The aim of this study was to determine whether patterns of atrophy on imaging could be useful to help predict underlying pathology in CBS.

Methods: This was a case-control study of 24 patients with CBS who had undergone MRI during life and came to autopsy. Pathologic diagnoses included frontotemporal lobar degeneration (FTLD) with TDP-43 immunoreactivity in 5 (CBS-TDP), Alzheimer disease (AD) in 6 (CBS-AD), corticobasal degeneration in 7 (CBS-CBD), and progressive supranuclear palsy in 6 (CBS-PSP). Voxel-based morphometry and atlas-based parcellation were used to assess atrophy across the CBS groups and compared to 24 age- and gender-matched controls.

Results: All CBS pathologic groups showed gray matter loss in premotor cortices, supplemental motor area, and insula on imaging. However, CBS-TDP and CBS-AD showed more widespread patterns of loss, with frontotemporal loss observed in CBS-TDP and temporoparietal loss observed in CBS-AD. CBS-TDP showed significantly greater loss in prefrontal cortex than the other groups, whereas CBS-AD showed significantly greater loss in parietal lobe than the other groups. The focus of loss was similar in CBS-CBD and CBS-PSP, although more severe in CBS-CBD.

Conclusions: Imaging patterns of atrophy in CBS vary according to pathologic diagnosis. Widespread atrophy points toward a pathologic diagnosis of FTLD-TDP or AD, with frontotemporal loss suggesting FTLD-TDP and temporoparietal loss suggesting AD. On the contrary, more focal atrophy predominantly involving the premotor and supplemental motor area suggests CBD or PSP pathology. *Neurology*® 2010;75:1879-1887

GLOSSARY

AAL = automated anatomic labeling; **AD** = Alzheimer disease; **CBD** = corticobasal degeneration; **CBS** = corticobasal syndrome; **CDR-SB** = Clinical Dementia Rating sum of boxes; **FDR** = false discovery rate; **FTLD** = frontotemporal lobar degeneration; **MMSE** = Mini-Mental State Examination; **PSP** = progressive supranuclear palsy; **ROI** = region of interest; **SMA** = supplemental motor area; **TDP** = TDP-43 immunoreactivity; **TIV** = total intracranial volume; **VBM** = voxel-based morphometry.

The corticobasal syndrome (CBS) is characterized by insidious onset and progressive asymmetric cortical and extrapyramidal dysfunction in the absence of an identifiable cause but usually due to an underlying neurodegenerative disorder.¹ Cortical abnormalities typically observed in CBS include ideomotor limb apraxia, cortical sensory loss, alien limb phenomenon, and myoclonus.² The CBS is not, however, associated with a specific pathology. We and others have demonstrated that CBS can be the presenting syndrome of a host of different pathologies, including corticobasal degeneration (CBS-CBD), progressive supranuclear palsy (CBS-PSP), Alzheimer disease (CBS-AD), and frontotemporal lobar degeneration (FTLD) with ubiquitin-only immunoreactive inclusions,³⁻⁵ which in the majority of cases show immunoreactivity to

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the TAR DNA binding protein of 43 kDa (CBS-TDP).^{6,7} Biomarkers are therefore needed to aid with prediction of pathology in subjects with CBS.

Patterns of asymmetric frontoparietal brain atrophy have been associated with both CBS⁸ and CBD pathology.^{9,10} However, we have previously demonstrated that the patterns of atrophy and hypometabolism identified in CBS-CBD differ from CBS-AD, with greater temporoparietal involvement observed in CBS-AD.^{4,11,12} It could therefore be hypothesized that imaging may provide a useful biomarker of pathology in CBS. The aim of this study was to expand on our previous study that assessed subjects with CBS-AD and CBS-CBD and to compare the atrophy patterns identified across all pathologic variants of CBS, including CBS-TDP, CBS-AD, CBS-CBD, and CBS-PSP, in order to determine whether imaging signatures can help predict underlying pathology in CBS.

METHODS Subjects. The Mayo Clinic, Rochester, MN, Autopsy Database was searched to identify all subjects who had been given a final clinical diagnosis of CBS from January 1, 1995, to January 1, 2010, had an antemortem volumetric MRI scan, and had died and come to autopsy ($n = 24$). Of the 24 identified cases, the pathologic diagnoses were CBD (CBS-CBD) in 7, PSP (CBS-PSP) in 6, FTLD-TDP (CBS-TDP) in 5, and AD (CBS-AD) in 6 cases. We have previously published imaging studies with different aims that have included 5 of the CBS-AD cases, 6 CBS-CBD cases,^{11,13} and 5 CBS-PSP cases¹⁰; all these groups, as well as the CBS-TDP group, have not previously been compared. All subjects with CBS-TDP with frozen tissue were screened for mutations in the progranulin gene (*GRN*) ($n = 4$), as previously described.¹³ The medical records of all subjects were reviewed by a neurodegenerative specialist (K.A.J.) to ensure that cases met published criteria for CBS¹ at the time of scan and to abstract clinical data. The 24 CBS cases were age- and gender-matched to 24 healthy living control subjects who were identified from the Mayo Clinic Alzheimer's Disease Research Center database.

Standard protocol approvals and patient consents. Informed consent was obtained from all subjects for participation in the studies, which were approved by the Mayo Clinic Institutional Review Board.

Neuropsychology. Neuropsychological test scores representing the domains of memory (Wechsler Memory Scale-Revised Logical Memory delayed recall percent retention), language (Boston Naming Test and Category Fluency Test), and executive function (Trail Making Test B and the Controlled Oral Word Association Test)¹⁴ performed closest to the time of MRI were collected.

Pathologic analysis. All subjects had undergone standardized neuropathologic examination using the recommended diagnos-

tic protocol for AD¹⁵ and were pathologically diagnosed by one of our experienced neuropathologists (J.E.P. or D.W.D.).

Frontotemporal lobar degeneration with TAR DNA binding protein 43 was diagnosed if there was neuronal loss and gliosis in frontal and temporal cortices, as well as ubiquitin and TDP-43 immunoreactive neuronal inclusions.¹⁶ Using published criteria,¹⁷ cases were diagnosed as having FTLD-TDP type 1 pathology if there were neuronal inclusions and short dystrophic neurites in layer II of neocortex and inclusions in the dentate gyrus of the hippocampus; type 2 if there were large and thick neurites throughout neocortex with absent-sparse inclusions; and type 3 if there were inclusions in neocortex or dentate granule cells of hippocampus and absent-sparse neurites. Pathologic diagnoses of PSP¹⁸ and CBD¹⁹ were made according to published diagnostic criteria. AD was diagnosed based on high probability of AD according to the NIA-Reagan criteria.²⁰

Asymmetry correction. CBS is asymmetric, whereby the greatest atrophy could be present in either left or right hemisphere.^{9,21} In this study a most severely affected (i.e., dominant) hemisphere for each subject was designated by K.A.J. (contralateral to the most affected limb) using clinical features at time of MRI, without reference to imaging. Each MRI was flipped in the X dimension so that the more severely affected hemisphere was positioned on the left side of the image in all subjects. This allowed us to assess patterns of gray matter atrophy in the dominant and nondominant hemispheres across all subjects.

Voxel-based morphometry. Patterns of cerebral atrophy were assessed using the automated and unbiased technique of voxel-based morphometry (VBM)²² implemented using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). All subject images were normalized and segmented into gray matter, white matter, and CSF using customized tissue probability maps and the unified segmentation²³ routine followed by the HMRP clean-up step. The customized prior probability maps were created from 116 subjects (35 controls and 81 subjects with FTLD-tau or FTLD-TDP²⁴). Gray matter images were modulated and smoothed at 8 mm full width at half maximum.

A full-factorial model was used to assess patterns of gray matter loss in each CBS group (CBS-TDP, CBS-AD, CBS-CBD, and CBS-PSP) compared to controls. Age and gender were included in the model as covariates. These analyses were assessed corrected for multiple comparisons using the false discovery rate (FDR) at $p < 0.001$, and uncorrected at $p < 0.001$. A conjunction analysis was performed to assess regions of loss that were common to all the CBS pathologic groups, and direct comparisons were performed between each CBS group and all other subjects with CBS, in order to identify regions of loss that are present in each pathologic group compared to the others. These analyses were performed uncorrected at $p < 0.001$ with age and gender included as covariates. In order to adjust for differences in disease severity, the direct comparisons were also performed including MMSE as a covariate.

Atlas-based parcellation. In order to investigate single subject-level regional differences in our different disease groups, an automated atlas-based parcellation technique was employed using SPM5 and the automated anatomic labeling (AAL) atlas²⁵ to generate gray matter volumes for specific regions of interest (ROIs) as previously published.¹² Briefly, the atlas²⁵ was normalized to the customized template and edited, transformed into MRI native anatomic space for each subject, and multiplied by a gray matter mask. Gray matter volumes were calculated for specific ROIs based on the VBM results: inferior and superior lat-

Table 1 Subject demographics^a

	Controls	CBS-TDP	CBS-AD	CBS-CBD	CBS-PSP	p Value
No.	24	5	6	7	6	
Male gender (%)	9 (38)	3 (60)	2 (33)	1 (14)	3 (50)	0.54
Education, y	15 (12-19)	13 (10-15)	16 (12-20)	12 (8-14)	13 (10-18)	0.07
Age at onset, y	NA	68 (49-74)	57 (55-70)	64 (41-72)	65 (52-79)	0.64
Age at MRI, y	67 (53-81)	71 (52-81)	60 (57-73)	68 (46-75)	69 (59-81)	0.53
Time from onset to death, y	NA	6 (3-9)	7 (6-9)	6 (5-8)	7 (4-9)	0.37
Time from onset to MRI, y	NA	3 (0-7)	2 (1-4)	4 (3-6)	5 (2-7)	0.17
Time from MRI to death, y	NA	2 (0-6)	5 (2-7)	1 (0-5)	2 (0-4)	0.08
UPDRS at MRI	NA	14 (9-18)	8 (2-11)	27 (6-32)	18 (7-25)	0.23
MMSE at MRI (/30)	29	22 (9-23)	26 (16-29)	20 (14-27)	27 (21-29)	<0.0001
CDR-SB at MRI (/18)	0 (0-0)	8 (6-11)	4 (1-10)	7 (7-7)	3 (1-9)	<0.0001
Dominant hemisphere left (%)	NA	3 (60)	2 (33)	5 (71)	3 (50)	0.57

Abbreviations: AD = Alzheimer disease; CBD = corticobasal degeneration; CBS = corticobasal syndrome; CDR-SB = Clinical Dementia Rating Scale sum of boxes; MMSE = Mini-Mental State Examination; NA = not applicable; PSP = progressive supranuclear palsy; TDP = TDP-43 immunoreactivity; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Data shown as median (range).

eral frontal lobes, supplemental motor area (SMA), lateral parietal lobe, medial and lateral temporal lobe, caudate, and insula. Total intracranial volume (TIV) was calculated by propagating a template-drawn TIV mask to the subject space as above, and then performing an erosion step to remove border voxels. All ROI volumes were corrected for TIV (volume/TIV) and converted into a *Z* score reflecting deviation from the control group average.

Statistics. Statistical analyses were performed using the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc., Cary, NC) with statistical significance set at $p < 0.05$. Kruskal-Wallis testing was used to assess differences in continuous variables across disease groups. If significant differences were observed then intergroup comparisons were performed using Mann-Whitney *U* test. Logistic regression was used to adjust for MMSE. χ^2 test was used to compare categorical variables across groups.

RESULTS Clinical and genetic findings. No significant differences were observed in any demographic features across groups (table 1). Significant differences were observed across all 5 groups, including controls, in Mini-Mental State Examination (MMSE)²⁶ and Clinical Dementia Rating sum of boxes (CDR-SB),²⁷ although no differences were observed across the 4 CBS pathologic groups ($p = 0.09$ for MMSE and $p = 0.26$ for CDR-SB).

Symptoms reported by the subjects with CBS varied across pathologies without any absolute discernible patterns (table e-1 on the *Neurology*[®] Web site at www.neurology.org). However, of those with CBS-TDP pathology, 60% reported behavioral and executive changes, which was uncommon in the other CBS groups. A family history of neurodegenerative disease was also identified in 80% of the subjects with CBS-TDP (one had a mutation in the *GRN* gene²⁸). Aphasia was a relatively common complaint across all CBS diagnoses, except for CBS-AD. Neu-

rologic examination findings documented limb apraxia in all 24 subjects with CBS and limb rigidity in almost 90% of subjects. Axial rigidity was uncommon. Cortical sensory loss was present across all groups, except for CBS-PSP. Limb myoclonus was most common in the subjects with CBS-AD but was also identified in 2 subjects with CBS-CBD. Apraxia of speech (AOS) was most common in CBS-CBD but was also identified in 2 subjects with CBS-PSP and 2 subjects with CBS-TDP. While AOS was identified in the subjects with CBS-CBD and subjects with CBS-PSP at presentation, AOS developed later in both subjects with CBS-TDP. Vertical supranuclear palsy was present in half of the subjects with CBS-PSP, as well as in one subject with CBS-CBD, but was absent in all subjects with CBS-AD and subjects with CBS-TDP.

No significant differences were observed across the CBS pathologic groups for any neuropsychological tests (table e-2), although there was a trend for a difference in Controlled Oral Word Association Test, with lowest scores observed in CBS-TDP and CBS-CBD ($p = 0.07$).

Pathologic findings. Detailed histopathologic examination (table e-1) of all CBS-TDP cases revealed TDP-43 immunoreactive neuronal cytoplasmic inclusions, and short dystrophic neurites in keeping with TDP-43 type 1 histology.¹⁷ All 5 cases also had neuronal intranuclear inclusions. All 6 pathologically confirmed CBS-AD cases had a Braak neurofibrillary tangle stage of VI^{11,29} and hence met criteria for high probability AD.²⁰ None of the CBS-TDP, CBS-CBD, or CBS-PSP cases, however, met criteria for high probability

Figure 1 Patterns of gray matter loss in each corticobasal syndrome (CBS) pathologic group compared to controls

Surface renderings showing regions of gray matter loss in the dominant and nondominant hemisphere of CBS-TDP, CBS-AD, CBS-CBD, and CBS-PSP compared to controls. All results are shown after correction for multiple comparisons using the false discovery rate (FDR) at $p < 0.001$, except for the results from the CBS-PSP group, which are shown uncorrected at $p < 0.001$. AD = Alzheimer disease; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; TDP = TDP-43 immunoreactivity.

AD. Lewy body disease was observed in 2 of the CBS-AD cases (one transitional and one diffuse),¹¹ but none of the CBS-TDP, CBS-CBD, or CBS-PSP cases.

Voxel-based morphometry. Patterns of gray matter loss in each CBS pathologic group compared to controls are shown in figure 1. Regions of loss survived correction for multiple comparisons using FDR $p < 0.001$ in all groups except for the PSP group. The PSP results are therefore shown uncorrected for multiple comparisons at $p < 0.001$. Widespread patterns of gray matter loss were identified in the dominant hemisphere in both the CBS-TDP and CBS-AD groups, although the patterns of loss differed across these 2 groups. CBS-TDP showed loss throughout medial and lateral frontal lobes and temporal lobes, with some involvement of parietal lobe in the dominant hemisphere. Similar, although less severe, patterns of loss were identified in the nondominant

hemisphere with frontal and posterior lateral temporal loss. In contrast, CBS-AD showed severe gray matter loss in lateral parietal lobe, precuneus, and posterior lateral temporal in the dominant hemisphere, with relative sparing of prefrontal cortex and medial temporal lobe. The nondominant hemisphere showed less severe involvement of the same regions. The patterns of loss observed in CBS-CBD were more focused and involved premotor cortex spreading to the inferior and superior posterior frontal lobes, and SMA. Similar patterns were identified in CBS-PSP, although they did not survive correction for multiple comparisons and there was a relative sparing of the inferior frontal lobe. Gray matter loss was observed in the insula, with mild loss in the caudate, in all CBS groups.

The conjunction analysis showed that the only regions of gray matter loss common to all CBS

Regions common to all CBS pathologies

Regions specific to CBS-TDP

Regions specific to CBS-AD

Dominant

Nondominant

Dominant

Nondominant

Dom. Nondom.

Results uncorrected $p < 0.001$

Surface renderings showing the results of 3 statistical comparisons: 1) regions of gray matter loss that were common to all CBS pathologic groups using a conjunction analysis, 2) regions of gray matter loss in the CBS-TDP group compared to all other CBS pathologic groups, and 3) regions of gray matter loss in the CBS-AD group compared to all other CBS pathologic groups. Results are shown uncorrected for multiple comparisons at $p < 0.001$. AD = Alzheimer disease; CBD = corticobasal degeneration; TDP = TDP-43 immunoreactivity.

pathologic groups were found in premotor cortex and insula in the dominant hemisphere and SMA in both the dominant and nondominant hemispheres (figure 2). Direct comparisons showed that CBS-TDP had greater loss in lateral prefrontal cortex in both dominant and nondominant hemispheres, and medial prefrontal cortex and posterior temporal lobe in the dominant hemisphere than the other CBS pathologies (figure 2). Conversely, CBS-AD showed greater loss predominantly in superior parietal lobe and precuneus in both dominant and nondominant hemispheres, and occipital lobe in the dominant hemisphere compared to the other CBS pathologies (figure 2). No regions were found to have greater loss in CBS-CBD and CBS-PSP when compared to all other CBS subjects. These group differences remained significant after adjustment for MMSE.

Atlas-based parcellation. Significant differences were observed across the CBS pathologic groups for all ROIs, except the nondominant SMA, lateral parietal lobe, and caudate, and both dominant and nondominant medial temporal lobes (table 2). On post hoc testing, CBS-TDP showed significantly greater

negative Z scores in dominant and nondominant inferior frontal lobe and insula, and dominant superior frontal lobe (figure 3), caudate, and lateral temporal lobe than the other 3 CBS pathologic groups (table 2). CBS-AD showed significantly greater negative Z scores in the dominant parietal (figure 3) and lateral temporal lobes compared to CBS-CBD and CBS-PSP, and had nonsignificant larger negative Z scores in the parietal lobe than CBS-TDP (table 2). Finally, CBS-CBD showed significantly larger negative Z scores in the dominant inferior frontal lobes, nondominant superior frontal lobes, and nondominant insula than CBS-PSP (table 2). All significant group differences persisted after adjustment for MMSE.

DISCUSSION This study has demonstrated that imaging patterns of gray matter loss differ in subjects with CBS dependent on the underlying pathology. The MRI were flipped to align the more severely affected hemispheres, allowing us to make conclusions concerning patterns of loss in both dominant and nondominant hemispheres. The CBS-TDP and CBS-AD groups were both associ-

Table 2 Average region of interest gray matter Z scores for each CBS pathologic group^a

Region and hemisphere	CBS-TDP	CBS-AD	CBS-CBD	CBS-PSP	p Value across all groups
Inferior frontal lobe					
Dominant	-4.5 (-5.0 to -3.6)	-1.2 (-2.2 to 0.5)	-1.9 (-2.6 to 0.9)	-0.2 (-1.1 to 1.7)	0.003** [¶]
Nondominant	-3.0 (-3.5 to -2.7)	-1.6 (-2.8 to -0.3)	-1.6 (-2.8 to -0.4)	-0.8 (-1.4 to 0.7)	0.005**
Superior frontal lobe					
Dominant	-4.7 (-5.5 to -3.4)	-2.2 (-2.9 to -0.9)	-2.4 (-2.7 to -0.8)	-1.2 (-2.8 to 1.0)	0.006**
Nondominant	-2.6 (-4.3 to -1.1)	-1.1 (-1.7 to -0.3)	-1.7 (-2.7 to 0.5)	-0.4 (-0.8 to 1.2)	0.009* [¶]
Supplemental motor area					
Dominant	-3.2 (-3.5 to -2.9)	-2.1 (-2.8 to -1.8)	-2.6 (-3.6 to -0.4)	-1.3 (-2.4 to 0.6)	0.010**
Nondominant	-2.6 (-3.1 to -1.5)	-1.9 (-2.2 to -0.2)	-1.5 (-2.0 to -1.1)	-1.3 (-2.8 to 0.7)	NS
Lateral parietal lobe					
Dominant	-3.7 (-5.0 to -2.7)	-4.3 (-5.0 to -2.1)	-1.4 (-4.3 to 0.4)	-1.7 (-2.9 to 0.4)	0.011** [¶]
Nondominant	-1.9 (-2.1 to 0.7)	-0.3 (-1.0 to 0.0)	-0.4 (-2.3 to 3.9)	2.0 (-1.2 to 4.8)	NS
Lateral temporal lobe					
Dominant	-4.0 (-5.2 to -3.4)	-2.4 (-4.9 to -1.2)	-1.2 (-1.9 to 1.2)	-0.1 (-1.9 to 2.0)	0.001** [¶]
Nondominant	-2.1 (-2.6 to -1.5)	-2.2 (-3.6 to -1.0)	-0.4 (-2.2 to 0.7)	0.3 (-1.0 to 1.1)	0.006* [¶]
Medial temporal lobe					
Dominant	-2.7 (-3.4 to -0.5)	-0.3 (-1.0 to 1.2)	-0.2 (-3.1 to 1.7)	0.4 (-4.9 to 1.2)	NS
Nondominant	-1.3 (-2.2 to -0.9)	-1.2 (-3.0 to 1.0)	-0.5 (-1.9 to 0.5)	-1.4 (-1.9 to 1.1)	NS
Insula					
Dominant	-5.9 (-6.7 to -4.4)	-2.3 (-4.6 to -1.1)	-1.9 (-4.8 to -1.0)	-1.0 (-4.4 to -0.2)	0.011**
Nondominant	-3.9 (-3.9 to -2.5)	-1.2 (-2.5 to -0.1)	-1.7 (-2.6 to 0.1)	-0.3 (-1.6 to 0.4)	0.004** [¶]
Caudate					
Dominant	-5.3 (-7.3 to -4.4)	-0.9 (-1.9 to -0.5)	-1.0 (-4.7 to 1.1)	-0.9 (-2.6 to -0.5)	0.02**
Nondominant	-2.3 (-3.2 to -0.5)	-1.0 (-2.6 to 1.3)	-0.4 (-1.3 to 0.9)	-0.7 (-1.8 to 0.3)	NS

Abbreviations: AD = Alzheimer disease; CBD = corticobasal degeneration; CBS = corticobasal syndrome; NS = not significant; PSP = progressive supranuclear palsy; TDP = TDP-43 immunoreactivity.

^a Data shown as median (range).

Significant difference between *CBS-TDP and CBS-AD, *CBS-TDP and CBS-CBD, *CBS-TDP and CBS-PSP, [¶]CBS-AD and CBS-CBD, [¶]CBS-AD and CBS-PSP, and [¶]CBS-CBD and CBS-PSP at $p < 0.05$.

ated with more widespread patterns of gray matter loss than the other groups, although there was overlap.

The CBS-TDP group was associated with imaging loss predominantly in the prefrontal cortex and posterior temporal lobes and showed significantly more loss in these regions in the dominant hemisphere than all the other groups. These patterns are typical of FTLD-TDP; we have previously shown that FTLD-TDP is associated with loss in the frontal and posterior temporal lobes.^{24,30,31} Parietal lobe atrophy can also be observed in FTLD-TDP, particularly when associated with a *GRN* mutation.^{13,32} One of the cases in our CBS-TDP cohort had a mutation in *GRN*, and 4 had a family history of neurodegenerative disease. Interestingly, all CBS-TDP cases were FTLD-TDP type 1, which has been linked to *GRN* mutations.³³ Familial CBS has also been previously associated with mutations in the *GRN* gene.^{34,35}

The CBS-AD group was associated with a predominantly posterior pattern of gray matter imaging

loss, involving parietal, posterior temporal, and occipital lobes, with sparing of medial temporal lobes, as we have previously noted.^{11,12} We have previously demonstrated using many of the same subjects that CBS-AD has greater loss in the temporoparietal lobes than CBS-CBD,¹¹ but this study extends these findings by showing that CBS-AD also has greater involvement of the temporoparietal lobes than CBS-PSP. When compared to all other CBS pathologies using VBM, the CBS-AD group only showed greater loss in the superior parietal and occipital regions, and not in the temporal lobe. This reflects the fact that temporoparietal loss was also a feature of CBS-TDP in this study, likely due to the familial nature of CBS-TDP as discussed above. These results therefore suggest that although temporoparietal atrophy is a signature of AD,¹² it may not be so helpful when assessing familial cases.

The CBS-CBD and CBS-PSP groups showed less widespread imaging patterns of loss, with both pre-

Figure 3 Scatterplots showing individual level volumetric data for 2 regions of interest

Z scores of the superior frontal lobe (A) and parietal lobe (B) in the dominant hemisphere are plotted for each corticobasal syndrome (CBS) pathologic group and controls. The boxes indicate the median and interquartile range of the distributions while the horizontal lines extending from the boxes stop at the most extreme data points. All CBS pathologic groups showed greater negative Z scores than controls for both regions. CBS-TDP showed the greatest negative Z score for the superior frontal lobe, whereas CBS-AD showed the greatest negative Z score for the parietal lobe. AD = Alzheimer disease; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; TDP = TDP-43 immunoreactivity.

dominantly affecting premotor cortex, posterior superior frontal lobe, and SMA. However, the degree of loss was less in CBS-PSP and the inferior frontal lobe appeared to be involved only in CBS-CBD. Pathologic changes have been observed in these posterior frontal regions in both CBD and PSP.³⁶ Brainstem pathology is also a feature of PSP.¹⁸ The fact that we did not observe gray matter changes in brainstem in our subjects with CBS-PSP concurs with the finding that pathology shifts to the cortex in cases with PSP pathology and atypical clinical syndromes.^{37,38} Although some of our subjects with

CBS-PSP had vertical supranuclear gaze palsy, none had falls and so would not meet research clinical criteria for PSP.³⁹

Premotor cortex, insula, and SMA imaging abnormalities identified in CBS-CBD and CBS-PSP were also identified in CBS-TDP and CBS-AD, and hence were found to be common to all the CBS pathologic groups. It is therefore likely that these regions are important to the clinical presentation of CBS. The SMA and premotor cortex have been shown to be associated with ideomotor apraxia in CBS⁴⁰ and, indeed, all subjects with CBS had limb apraxia in this study, which is one of the fundamental clinical hallmarks of CBS. The caudate nucleus showed mild loss across all the CBS pathologic groups, although was less severely affected than the other regions and was not found to be common to all groups in the conjunction analysis. An asymmetric imaging pattern was also observed across all the CBS pathologic groups, which is consistent with previous clinical and imaging studies.^{9,10,21} The additional regions of loss identified in CBS-TDP and CBS-AD are less likely to be contributing to the CBS phenotype, and more likely reflect the constellation of additional symptoms that occur together with CBS. For example, the presence of prefrontal loss in CBS-TDP fits with the fact that behavioral changes and executive dysfunction were common in this group. Nevertheless, these additional regions could be useful in helping to predict the presence of these pathologies in patients with a CBS phenotype.

Assessing atrophy patterns separately in each of the different pathologies that can underlie CBS was an important advantage of our study. One of our earlier studies lumped different pathologies together and failed to identify any differences in atrophy on visual inspection between CBS-CBD and CBS with other pathologies.²¹ Although the number of subjects in each pathologic group was relatively small in the current study, we were still able to identify significant differences across groups. Thus, widespread and severe patterns of atrophy in the context of CBS should point to a pathologic diagnosis of either FTLD-TDP or AD, with frontotemporal loss suggesting FTLD-TDP and temporoparietal loss suggesting AD. More focal patterns of loss involving premotor cortex and SMA would be more suggestive of underlying CBD or PSP pathology, with sparing of the inferior frontal lobe and presence of vertical supranuclear palsy suggesting PSP. A trend for difference in MMSE was observed across groups, although we demonstrated that group differences remained after adjustment for MMSE score, showing that they do not simply reflect more impaired disease severity. Although the VBM analyses were performed at the group level, the

subject level data suggest that these findings could be useful in predicting pathology in individual subjects, as well as aid in the identification of patients with CBS for appropriate clinical trial inclusions/exclusion for future interventions targeting β -amyloid, tau, or TDP-43.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Keith A. Josephs.

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DISCLOSURE

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