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Anatomical Differences between CBS-Corticobasal degeneration and CBS-Alzheimer's Disease

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Abstract

We compare patterns of grey matter loss on MRI in subjects presenting as corticobasal syndrome (CBS) with Alzheimer disease pathology (CBS-AD) to those presenting as CBS with corticobasal degeneration pathology (CBS-CBD). Voxel-based morphometry was used to compare patterns of grey matter loss in pathologically confirmed CBS-AD subjects (n=5) and CBS-CBD subjects (n=6) to a group of normal controls (n=20), and to each other. Atlas based parcellation using the automated anatomic labeling atlas was also utilized in a region-of-interest analysis to account for laterality. The CBS-AD subjects were younger at the time of scan compared to CBS-CBD subjects (median: 60 years vs 69; P=0.04). After adjusting for age at time of MRI scan, the CBS-AD subjects showed loss in posterior frontal, temporal, and superior and inferior parietal lobes, while CBS-CBD showed more focal loss predominantly in the posterior frontal lobes, compared to controls. In both CBS-AD and CBS-CBD groups there was basal ganglia volume loss, yet relative sparing of hippocampi. On direct comparisons between the two subject groups, CBS-AD showed greater loss in both temporal and inferior parietal cortices than CBS-CBD. No regions showed greater loss in the CBS-CBD group compared to the CBS-AD group. These findings persisted when laterality was taken into account. In subjects presenting with CBS, prominent temporoparietal, especially posterior temporal and inferior parietal, atrophy may be a clue to the presence of underlying AD pathology.

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AUTHORS ROLE

1. Research project: A. Conception, B. Organization, C. Execution
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique
3. Manuscript: A. Writing of the first draft, B. Review and Critique

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Keywords

Voxel based morphometry; Alzheimer's disease; Corticobasal syndrome; Corticobasal degeneration; Region-of-Interest

INTRODUCTION

The corticobasal syndrome (CBS) can be characterized by asymmetric dystonia, Parkinsonism, and limb apraxia with supportive findings of cortical and basal ganglia dysfunctions such as cortical sensory loss, alien-limb phenomenon, and myoclonus^{1, 2}. Unfortunately, the predictive value of this syndrome for underlying pathology is poor-average. In one study assessing clinicopathological associations of CBS and underlying pathology, CBS was associated with six different pathologies, the most common of which was corticobasal degeneration (CBD)³. More recently, it has become apparent that a significant number of subjects with CBS have underlying Alzheimer's disease (AD) pathology^{4, 5}. We previously compared clinical and neuropsychological features in subjects presenting as CBS and having CBD pathology (CBS-CBD) with subjects presenting with CBS but having AD pathology (CBS-AD)⁴. Both groups had almost identical clinical and neuropsychological profiles, although those with CBS-AD were younger at onset, more likely to have myoclonus, and less likely to have tremor. In that study, single photon emission computer tomographic (SPECT) scanning suggested that parietal lobe hypoperfusion may be more associated with CBS-AD. Since that publication⁴, we have had more subjects with CBS-AD and CBS-CBD come to autopsy, many of whom had completed a volumetric head MRI prior to death.

Therefore, in this study we aimed to compare patterns of brain volume loss on MRI in our CBS-CBD and CBS-AD subjects to determine whether MRI could be a useful biomarker in predicting underlying AD versus CBD pathology, in CBS. Given our previous SPECT findings⁴, we hypothesized that atrophy in the parietal lobe would be associated with CBS-AD, but not with CBS-CBD.

METHODS

Subjects

We have previously described our search criteria in detail⁴. Informed consent was obtained from each subject in the study. Briefly, the Mayo Clinic Autopsy Database was searched to identify all subjects with a pathologic diagnosis of CBD or AD and CBS from January 1st, 1990 to June 31st, 2009. All subjects had been examined pathologically by one of two experienced neuropathologists (JEP, DWD) and diagnosed as CBD or AD based on published criteria^{6, 7}. A total of 20 subjects, CBS-AD (n=5) and CBS-CBD (n=15), were identified not including subjects with pathologically confirmed CBD that had pure apraxia of speech or non-fluent aphasia at presentation, without any extrapyramidal features at onset⁸. We excluded subjects with pure apraxia of speech and non-fluent aphasia, since those subjects would not meet criteria for CBS at presentation^{1, 2}. We were interested only in subjects with "typical" CBS in which extrapyramidal features are present^{1, 2}, since these are the subjects that we find difficult to predict CBD as opposed to AD pathology. All 20 subjects had been given a clinical diagnosis of CBS and met published criteria for diagnosing CBS at presentation^{1, 2}. In order to be included in this study, subjects had to have completed at least one volumetric head MRI scan that could be used for imaging analyses. Eleven of the 20 subjects, 6 CBS-CBD and 5 CBS-AD, had at least one volumetric head MRI scan.

The study has been approved by the Mayo Institutional Review Board.

The 11 subjects in this study were age-matched to 20 healthy controls initially recruited into the Mayo Alzheimer's Disease Research Center or Alzheimer's disease Patient Registry.

Pathological analysis

All subjects underwent standardized neuropathological examination using the recommended diagnostic protocol for AD⁷. Pathological diagnoses were conducted by one of our experienced neuropathologists (JEP or DWD). After removal, the brain was divided into right and left hemi-brains. The left hemi-brain was fixed in 10% buffered formaldehyde for 7 to 10 days, and then sectioned. Samples were processed in paraffin and stained with hematoxylin and eosin and modified Bielschowsky silver impregnation, and immunostained with antibodies to β -amyloid (clone 6F/3D, 1:10 dilution; Novocastra Vector Labs, Burlingame, CA), tau (clone AT8, 1:1,000 dilution; Endogen, Woburn, MA), alpha-synuclein (clone LB509, 1:200 dilution; Zymed, San Francisco, CA), neurofilament (DAKO clone 2F11, 1:75 dilution; DAKO, Carpinteria, CA), ubiquitin (DAKO polyclonal, 1:100 dilution), and the TAR DNA-binding protein 43 (1:8000; ProteinTech group, Chicago, IL). In each case Braak staging was performed using Bielschowsky silver stain (Braak and Braak, 1991).

A pathological diagnosis of AD was made based on high probability of AD according to the NIA Reagan criteria⁹. A pathological diagnosis of CBD was made based on published criteria for the pathological diagnosis of CBD⁶.

Voxel-based morphometry

All subjects underwent a standardized protocol head MRI scan at 1.5T that included a T1-weighted 3-dimensional spoiled gradient echo sequence (22×16.5cm or 24×18.5cm FOV, 25° flip angle, 124 contiguous 1.6mm thick coronal slices). Patterns of cerebral atrophy were assessed using the automated and unbiased technique of voxel-based morphometry (VBM)¹⁰. An optimized method of VBM was applied using both customized templates and prior probability maps, implemented using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). The processing steps were performed as previously described^{11, 12}. Briefly, all images were normalized to a customized template. The spatial normalization was optimized by normalizing the grey matter images to the customized grey matter template. Images were segmented using customized prior probability maps, modulated, and smoothed with an 8mm full-width at half-maximum smoothing kernel.

A single subject condition and covariate model was used to compare the smoothed modulated gray matter images between the CBS-CBD subjects and controls, and between the CBS-AD subjects and controls. Age and gender were included in the statistical model as nuisance variables in order to correct for potential confounds that could affect the outcome. The analyses were corrected for multiple comparisons using the false discovery rate (FDR)¹³ correction at $p < 0.05$. Direct comparisons were also performed between the CBS-CBD and CBS-AD subjects in order to identify regions that showed greatest loss in the CBS-CBD compared to the CBS-AD subjects, and conversely to identify regions that showed greatest loss in the CBS-AD subjects compared to the CBS-CBD subjects (uncorrected at $p < 0.001$). Inclusive masking procedures were also used to identify regions of grey matter loss common to both the CBS-CBD and CBS-AD groups when compared to controls, and exclusive masking was used to identify regions of loss present only in the CBS-CBD subjects, and regions of loss present only in the CBS-AD subjects, when compared to controls. These analyses were assessed at $p < 0.05$ corrected for multiple

comparisons using the FDR, with a threshold of $p < 0.001$ uncorrected for multiple comparisons for the masking procedure.

Atlas-based parcellation

In order to investigate subject-level regional differences in our different disease groups an atlas-based parcellation technique was employed using SPM5 and the automated anatomic labeling (AAL) atlas¹³ to generate grey matter volumes for specific regions-of-interest (ROIs) as previously published¹⁴. The following ROIs were analyzed: temporoparietal cortex, hippocampus, medial and lateral frontal lobe, insula and basal ganglia. In addition, 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. In order to account for the asymmetric nature of CBS, ROI volumes were analyzed separately for the “dominant” and “non-dominant” cerebral hemispheres, determined from the main affected limb¹⁵.

Statistical Analysis

Statistical analyses were performed using the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc., Cary, NC, USA) with statistical significance set at $p < 0.05$. Mann-Whitney U test was used to analyze differences in age of onset, disease duration, age at MRI scan, time from onset to scan, Mini Mental State Examination (MMSE)¹⁶, Clinical Dementia Rating Scale sum of boxes (CDR-SB)¹⁷, Unified Parkinson's Disease Rating Scale (UPDRS) total motor scores¹⁸, and the questionnaire version of the neuropsychiatric inventory (NPI-Q)¹⁹ between the CBS-CBD and CBS-AD groups. Fisher's exact test was used to compare gender differences across both groups. Logistic regression analysis was used to determine the ability of dominant and non-dominant ROI volumes to predict pathology, adjusting for age at MRI scan.

RESULTS

Individual subject demographics and presenting clinical features of all 11 CBS subjects are shown in Table 1. Of these 11 subjects with volumetric MRI scans, eight were previously reported in our clinical and neuropsychological comparison between CBS-CBD and CBS-AD⁴. Statistical comparison between the CBS-CBD and CBS-AD groups (Table 2) revealed that subjects with CBS-AD were more educated than CBS-CBD subjects (16 vs. 12 years of education; $p = 0.04$) and were younger at the time of MRI scan (60 yrs. vs 69; $p = 0.04$) although both groups had similar time from onset to time of MRI scan. There was no difference in disease severity measures of both cognitive (MMSE¹⁶ and CDR-SB¹⁷) and motor (UPDRS total motor score¹⁸) function or on any of the neurobehavioral sub-measures or total severity score of the NPI-Q¹⁹.

Pathological Findings

All 5 pathologically confirmed CBS-AD subjects had a Braak neurofibrillary tangle stage of VI and hence met criteria for high probability AD. The CBS-CBD subjects however all met criteria for low probability AD. Braak neurofibrillary tangle stage in the CBS-CBD subjects ranged from 0-III. Two of the CBS-AD subjects had Lewy body disease, one Braak and Braak Lewy body stage VI and the other Lewy body stage IV²⁰. None of the six CBS-CBD subjects had Lewy body disease. There were no atypical clinical features in the 2 CBS-AD subjects with Lewy body disease up to the time of MRI scans. However, in the one subject with Braak Lewy body stage VI, visual hallucinations were noted to occur 6 years after disease onset. None of the subjects had rapid eye movement sleep behavior disorder (RBD) by history.

Imaging results

The CBS-CBD subjects showed grey matter loss predominantly in the superior premotor cortices spreading to the posterior superior, middle and inferior frontal lobes, compared to controls (Figure 1). Some loss was also observed in the superior parietal lobes, basal ganglia and thalamus. In contrast, the CBS-AD subjects showed a more widespread pattern of grey matter loss when compared to controls predominantly involving posterior regions of the brain (Figure 1). Grey matter loss was observed throughout the parietal lobe (superior and inferior), and in the inferior and lateral temporal lobe, posterior frontal lobe, posterior cingulate, basal ganglia, thalamus, insula and occipital lobe. There was a relative sparing of the hippocampi in both groups (Figure 1). Inclusive masking procedures showed that grey matter loss common to both the CBS-CBD and CBS-AD subjects was identified in the superior premotor cortex, posterior superior frontal lobes, superior parietal lobes, putamen and caudate nucleus (Figure 1). The same regions were identified when a statistical conjunction was performed. Exclusive masking procedures showed that the CBS-CBD subjects had greater involvement of the posterior frontal lobes than the CBS-AD patients. Conversely, grey matter loss in the CBS-AD subjects was greater throughout the parietal, temporal and occipital lobes than the CBS-CBD subjects (Figure 1).

On direct comparison the CBS-AD subjects showed greater loss than the CBS-CBD subjects predominantly in bilateral posterior temporal and inferior parietal lobes (Figure 2). No regions showed greater loss in the CBS-CBD subjects compared to the CBS-AD subjects.

The results of the atlas based parcellation are shown in Table 3. The right hemisphere was dominant in three of five CBS-AD subjects but only in one of six CBS-CBD subjects ($p=0.19$). After accounting for laterality, logistic regression analysis showed that only dominant temporoparietal ($p=0.001$) and non-dominant temporoparietal ($p=0.01$) regions predicted underlying pathology.

DISCUSSION

Using the automated and unbiased technique of VBM, we found differences in atrophy patterns in CBS-AD compared to CBS-CBD. These differences were more evident in the dominant rather than non-dominant hemisphere. The finding has important implications as it suggests that MRI may be a useful tool to aid in the differentiation of CBS-CBD from CBS-AD.

It has been long known that subjects with CBD pathology show a pattern of atrophy affecting predominantly posterior frontal, as well as superior parietal lobe^{15, 21–23}. Indeed, with VBM we identified this exact pattern of loss in our CBS-CBD subjects²⁴. What is now apparent from this study is that subjects with CBS-AD also show posterior frontal and superior parietal atrophy, however they show much more widespread atrophy, also affecting inferior parietal, posterior temporal and even occipital cortex. In fact these patterns are similar to those that have been reported in posterior cortical atrophy (PCA)²⁵. Therefore, identifying a pattern of posterior frontal and superior parietal atrophy will not allow the differentiation of CBS-CBD from CBS-AD. Actually, posterior frontal and superior parietal atrophy can also be found in subjects with other degenerative pathologies such as progressive supranuclear palsy and frontotemporal lobar degeneration¹⁵. More important, however, appears to be the presence or absence of posterior temporal and inferior parietal (temporoparietal) atrophy accompanying the CBS. The findings from this study suggest that the presence of temporoparietal atrophy is associated with CBS-AD but not CBS-CBD and hence could be a useful way, even a potential biomarker, to differentiate CBS-CBD from CBS-AD. Given that CBS subjects can have either left or right sided dominant disease, we utilized an ROI analysis that allowed us to account for laterality. The finding from that

analysis suggested that temporoparietal atrophy of the dominant hemisphere (more affected cerebral hemisphere according to more affected contralateral limbs) is a better predictor than the non-dominant hemisphere.

It is not surprising that the subcortical grey nuclei were affected almost identically in the CBS-CBD and CBS-AD subjects. Both groups showed involvement of the basal ganglia which is keeping with the fact that all our subjects met criteria for CBS. We also did not find differences in hippocampal volume loss between both groups with relative preservation of the hippocampi compared to controls which is in keeping with our previous study demonstrating relative preservation of episodic memory on neuropsychological testing in both groups.⁴ We also did not find significant differences in thalamus or insula regions which have been shown to be affected pathologically in CBD^{6, 26}. Therefore, assessing subcortical grey matter loss in basal ganglia, thalamus, insula and hippocampi is less likely to be helpful in differentiating CBS-CBD from CBS-AD.

The findings from this study cannot be explained by differences in demographic features. Although there was an age difference at the time of MRI scan, we adjusted for age in our VBM and ROI analyses. It is also unlikely that the CBS-AD subjects were more severe, accounting for the more widespread pattern of atrophy, as there were no significant differences in any of the cognitive or motor measures of disease severity. Furthermore, those with CBS-AD had less severe cognitive and motor scores with a trend for the CBS-AD subjects to have less severe UPDRS scores ($p=0.09$). In addition, the more severe pattern of loss in the CBS-AD group cannot be explained by longer disease duration as the CBS-AD group had a shorter time from onset to scan, although again, not significantly different.

Two CBS-AD subjects had Lewy body disease which is also unlikely to have affected the patterns of grey matter loss observed, as we have previously shown that Lewy body disease is associated with minimal grey matter loss^{27, 28}. One of these two CBS-AD subjects did have late onset visual hallucinations which may have been secondary to the presence of Lewy bodies since hallucinations is a common feature of Lewy body disease²⁹. Lewy body disease in the presence of AD has been reported in another subject presenting as CBS also having visual hallucinations³⁰. Therefore, the presence of visual hallucinations in a subject with CBS may be a clinical clue to underlying Lewy body disease and hence AD pathology.

The results of this study should not be generalized to subjects with asymmetric cortical signs and symptoms, without motor signs and symptoms that could have CBD and AD pathology, for example, subjects who may present with pure apraxia of speech⁸, non-fluent aphasia or another asymmetric cortical syndrome. This is important since even pathologically confirmed CBD subjects with dominant extrapyramidal signs will have a somewhat different pattern of a brain volume loss compared to CBD subjects in which cognitive impairment is the dominant feature²⁴. The strengths of this study are that all subjects had histologic confirmation of the pathologies, and the techniques of VBM and atlas based parcellation which are automated and unbiased. The findings from this study will need to be replicated in a larger autopsy confirmed cohort with a prospective design that takes into account neuropsychological measures that are sensitive and specific to temporoparietal dysfunction.

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Dr. Whitwell reports no disclosures.

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Figure 1.

Regions that showed greater grey matter loss in the CBS-AD and CBS-CBD subjects compared to controls. (A) 3D renders show the results of inclusive and exclusive masking procedures. Regions of grey matter loss common to the CBS-CBD and CBS-AD subjects when compared to controls are shown in red, regions that only show loss in the CBS-AD subjects are shown in green, and regions that only show loss in the CBS-CBD subjects are shown in blue. (B) Coronal slices illustrating involvement of the basal ganglia and sparing of the hippocampus in the CBS-CBD and CBS-AD subjects when compared to controls. All results are shown after correction for multiple comparisons using the false discovery rate at $p < 0.05$.

Figure 2. Regions that showed greater grey matter loss in the CBS-AD subjects compared to the CBS-CBD subjects, shown on 3D renders of the brain and representative coronal and sagittal slices. Results are shown uncorrected at $p < 0.001$.

Table 1

Demographics and presenting features of CBS-AD and CBS-CBD

Subject	Diagnosis	Sex	Age at onset	Age at death	Illness Duration	Presenting clinical symptoms
1	CBS-CBD	F	62	75	6	Difficulty holding objects with left hand
2	CBS-CBD	F	72	80	8	Difficulty with writing and coordinated movements of right upper and lower extremities and falls
3	CBS-CBD	F	61	67	6	Progressive incoordination, stiffness, pain and tremulousness of right > left limbs
4	CBS-CBD	F	64	69	5	Right sided stiffness and difficulty with speech and language
5	CBS-CBD	F	68	74	6	Difficulty sewing, unsteadiness walking and visuospatial problems
6	CBS-CBD	F	63	69	6	Hypophonia, tremulousness of right hand, poor balance and aphasia
7	CBS-AD	M	59	65	6	Odd behaviors of the left arm and problems visual perceptual problems
8	CBS-AD	M	56	65	9	Difficulty with technical skills such as with using familiar tools
9	CBS-AD	F	70	76	6	Odd left hand posture & tremor, Parkinsonism, difficulty seeing objects in front of her, and memory loss
10	CBS-AD	F	62	71	9	Difficulty using the right hand for skilled movements
11	CBS-AD	F	55	61	6	Dragging right foot, right foot would turn out with walking and tripping

AD= Alzheimer's disease, CBS = corticobasal syndrome, CBD = corticobasal degeneration Median disease duration

Table 2

Statistical comparison of CBS-AD and CBS-CBD features

	CBS-CBD	CBS-AD	Controls
n	5	6	20
Female	3 (60%)	6 (100%)	10 (50%)
Education*	12 (8–14)	16 (12–20)	14 (12–20)
Age of Onset, yrs	66 (61–72)	59 (55–70)	NA
Age at death, yrs.	72 (67–80)	65 (61–76)	NA
Illness duration, yrs.	6 (5–8)	6 (6–9)	NA
Age at MRI scan, yrs.*	69 (66–75)	60 (59–73)	67 (55–83)
Time from onset to time of MRI	4 (3–6)	2 (2–4)	NA
UPDRS total motor score at time of MRI	27 (6–32)	8 (2–11)	0 (0–1)
MMSE score at time of MRI	17 (14–23)	27 (16–29)	29 (25–30)
CDR-SB	7 (7–7)	4 (1–10)	0 (0–0)
NPI-Q	6 (2–6)	6 (0–20)	0 (0–4)
NIA-Reagan	Low (100%)	High (100%)	NA
Braak neurofibrillary tangle Stage	I (0–III)	VI (VI–VI)	NA

Data shown as median and range; CDR-SB = Clinical Dementia Rating Scale sum of boxes; MMSE = Mini Mental State Examination; NPI-Q = questionnaire version of the neuropsychiatric inventory; UPDRS = Unified Parkinson's disease Rating Scale; NA= not applicable

*
p<0.05 when CBS-CBD and CBS-AD were compared.

Table 3

Region of interest (ROI) volumes for the dominant and non-dominant hemisphere in CBS-CBD and CBS-AD

ROI	Hemisphere	CBS-CBD	CBS-AD	Controls [†]
Temporoparietal	Dominant [*]	0.89 (0.80–1.09)	0.80 (0.68–0.87)	1.06
	Non-dominant [*]	0.98 (0.93–1.20)	0.82 (0.74–1.05)	
Hippocampus	Dominant	0.27 (0.19–0.30)	0.26 (0.22–0.29)	0.27
	Non-dominant	0.25 (0.22–0.29)	0.27 (0.23–0.27)	
Medial frontal	Dominant	1.04 (0.82–1.16)	1.03 (0.88–1.26)	1.11
	Non-dominant	0.99 (0.89–1.22)	1.06 (0.97–1.24)	
Lateral frontal	Dominant	2.11 (1.78–2.53)	2.25 (1.85–2.40)	2.65
	Non-dominant	2.22 (1.99–2.61)	2.38 (2.10–2.62)	
Insula	Dominant	0.40 (0.28–0.50)	0.40 (0.29–0.46)	0.51
	Non-dominant	0.42 (0.37–0.46)	0.46 (0.40–0.50)	
Basal ganglia	Dominant	0.41 (0.33–0.60)	0.40 (0.35–0.43)	0.45
	Non-dominant	0.46 (0.36–0.50)	0.40 (0.38–0.48)	

Data shown as median and range for CBS; ROI volumes are expressed as (ROI volume/TIV)*100

^{*} Significantly different when CBS-CBD and CBS-AD were compared.[†] Average left and right hemisphere ROI volumes are shown for controls as comparison