

Clinical and pathologic features of cognitive-predominant corticobasal degeneration

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Abstract

Objective

To describe clinical and pathologic characteristics of corticobasal degeneration (CBD) with cognitive predominant problems during the disease course.

Methods

In a series of autopsy-confirmed cases of CBD, we identified patients with cognitive rather than motor predominant features (CBD-Cog), including 5 patients thought to have Alzheimer disease (AD) and 10 patients thought to have behavioral variant frontotemporal dementia (FTD). We compared clinical and pathologic features of CBD-Cog with those from a series of 31 patients with corticobasal syndrome (CBD-CBS). For pathologic comparisons between CBD-Cog and CBD-CBS, we used semiquantitative scoring of neuronal and glial lesion types in multiple brain regions and quantitative assessments of tau burden from image analysis.

Results

Five of 15 patients with CBD-Cog never had significant motor problems during their disease course. The most common cognitive abnormalities in CBD-Cog were executive and visuospatial dysfunction. The frequency of language problems did not differ between CBD-Cog and CBD-CBS. Argyrophilic grain disease, which is a medial temporal tauopathy associated with mild cognitive impairment, was more frequent in CBD-Cog. Apathy was also more frequent in CBD-Cog. Tau pathology in CBD-Cog was greater in the temporal and less in perirolandic cortices than in CBD-CBS.

Conclusion

A subset of patients with CBD has a cognitive predominant syndrome than can be mistaken for AD or FTD. Our findings suggest that distribution of tau cortical pathology (greater in temporal and less in perirolandic cortices) may be the basis of this uncommon clinical variant of CBD.

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Glossary

AD = Alzheimer disease; AGD = argyrophilic grain disease; bvFTD = behavioral variant frontotemporal dementia; CBD = corticobasal degeneration; CBD-Cog = cognitive predominant corticobasal degeneration; CBS = corticobasal syndrome; DAB = 3,3'-diaminobenzidine; FTD = frontotemporal dementia; NFT = neurofibrillary tangle; SNP = single nucleotide polymorphism.

Corticobasal degeneration (CBD) is a distinctive neurodegenerative tauopathy with a range of clinical presentations.¹ The neuropathologic criteria for CBD are presence of neuronal, glial (astrocytic plaques²), and tau threads in both gray and white matter of neocortex and striatum, accompanied by ballooned neurons and focal neuronal loss in the neocortex and in the substantia nigra.³ CBD was originally associated with a movement disorder, and one of the characteristic clinical presentations of CBD is asymmetric rigidity and apraxia, often with dystonia and alien limb sign, a presentation referred to as the corticobasal syndrome (CBS).^{4,5} Whereas CBS is one of the most frequent clinical presentations of CBD, there are other syndromes that are nearly as frequent in autopsy series of CBD.^{6,7} Current clinical criteria for CBD describe 4 major clinical phenotypes of CBD: corticobasal syndrome (CBD-CBS), frontal-behavioral-spatial syndrome, nonfluent/agrammatic primary progressive aphasia, and Richardson syndrome or progressive supranuclear palsy syndrome.¹ In a survey of brain banks, 8.1% of CBD cases had antemortem clinical diagnoses of Alzheimer type dementia (CBD-AD).¹ Given the frequency of Alzheimer disease (AD) in the general population, CBD-AD was excluded given concerns that including a cognitive predominant phenotype would have an unacceptably high false-positive rate. Nevertheless, cognitive deficits, which may precede motor signs by a number of years, are increasingly recognized as a feature of some cases of CBD.⁸ In support of this is the fact that cognitive-predominant or pure cognitive presentations of CBD are reported in autopsy series of CBD.^{9,10} Neuropathologic correlates of cognitive predominant presentations of CBD, including CBD-AD, have not been systematically studied. As disease-modifying therapies are developed, including 4R tau as a therapeutic target,^{11,12} it will be important to differentiate underlying pathology. In the present study, we focused on clinicopathologic characteristics of cognitive predominant CBD (CBD-Cog). We compared CBD-Cog with CBD-CBS with respect to a range of clinical and pathologic parameters, including quantitative burden of tau pathology using digital imaging methods, as well as distribution of neuronal and glial lesions and presence of comorbid pathologies, such as argyrophilic grain disease (AGD).^{13,14}

Methods

Case materials

All autopsy cases were submitted to the brain bank for neurodegenerative disorders at Mayo Clinic in Jacksonville, Florida. The left or right hemibrain was fixed in 10% formalin,

and the opposite hemibrain was frozen at -80°C . In this study, left or right hemibrain were evaluated in all cases, but most were the left side (1 of 15 CBD-Cog and 3 of 31 CBD-CBS were the right side). Clinical information (age at death, sex, clinical diagnosis, disease duration, and family history) was obtained from available medical records.

Demographics

A total of 217 cases with a neuropathologic diagnosis of CBD were identified in the brain bank for neurodegenerative disorders at Mayo Clinic in Jacksonville between 1998 and 2018. Our intent was to try to understand the pathologic underpinnings of cognitive predominant CBD. We excluded 89 cases of CBD with antemortem diagnosis or differential diagnosis of progressive supranuclear palsy, the most common misdiagnosis of CBD.⁷ Given the concern that cognitive impairment could be linked to comorbid pathologic processes strongly associated with dementia (e.g., Alzheimer type pathology), we excluded cases that harbored such pathologies. We excluded 41 CBD cases with concomitant intermediate to high likelihood AD (operationally defined as Braak neurofibrillary tangle (NFT) stage III or greater and Thal amyloid phase greater than 0),¹⁵ as well as other disease processes associated with cognitive and behavioral impairments, including hippocampal sclerosis,¹⁶ severe cerebrovascular pathology, and cases with cortical Lewy bodies (table e-1, doi.org/10.5061/dryad.1vhhmqp5). AGD was detected in over 40% of CBD cases and was not excluded, because there is little evidence to suggest that AGD is strongly associated with dementia, except in rare cases with diffuse neocortical argyrophilic grain disease.¹⁷ In Braak's original series, AGD was associated with a slowly progressive amnesic syndrome,¹⁴ while other studies have noted association of AGD with psychiatric symptoms.¹⁸ Given these uncertainties, we had no a priori reason to exclude cases with AGD. The CBD-Cog cases were subsequently matched to CBD-CBS, with respect to demographic features (sex, age at onset, age at death, disease duration). Given that many of the cases evaluated in the brain bank were referred from outside sources, we limited study to only patients with reliable medical records including at least one cognitive or neurobehavioral assessment. The final cohort of CBD-Cog included 15 patients. Of these 15 patients, the final clinical diagnosis was AD (CBD-AD) in 5 patients and frontotemporal dementia (FTD) (CBD-FTD) in 10 patients. All 15 patients had prominent cognitive, not motor, symptoms. Adjudication of suitability for inclusion was made by thorough review of medical records by 2 neurologists and 1 psychologist. The psychologist and neurologists

reviewed records and assigned cognitive assessments independently and blinded to final classification. Thirty-one cases with a final clinical diagnosis of CBS (CBD-CBS) were selected for comparison, matching CBD-Cog as closely as possible to CBD-CBS for age, sex, age at onset, age at death, and disease duration, as well as for Braak NFT stage¹⁹ and Thal amyloid phase²⁰ (table 1).

Clinical assessment of cognitive dysfunction

Information about first symptoms and signs as well as results of neuropsychological testing and cognitive screening were obtained from the medical records. Historical information and results of neurologic evaluations were obtained from experienced clinicians (neurologists, neuropsychologists, behavioral neurologists, or geriatricians; table e-2, doi.org/10.5061/dryad.1vvhmgqp5) and all had documented detailed neurologic examination. Neuropsychological evaluations on

most patients (CBD-Cog n = 8, CBD-CBS n = 11) were conducted by licensed psychologists and included standardized measures assessing global cognitive function, naming, memory, executive functioning, and visuospatial ability (table e-3, doi.org/10.5061/dryad.1vvhmgqp5). A clinical diagnosis of dementia was considered after integrating results from the clinical and cognitive assessments. Mini-Mental State Examination, Montreal Cognitive Assessment, or Kokmen Short Test of Mental Status were available for all patients.

In order to assign CBD-FTD, we followed the 1998 Nearly criteria⁹ for the clinical diagnosis of FTD, focusing on prominent cognitive problems, including behavioral and progressive aphasia. CBD-FTD participants also conformed to international consensus criteria for behavioral variant FTD (bvFTD),¹⁰ including the following symptoms: (1) disinhibition, (2) apathy, (3) loss of sympathy or empathy, (4)

Table 1 Comparison of cognitive predominant corticobasal degeneration (CBD-Cog) with corticobasal degeneration with corticobasal syndrome (CBD-CBS)

	CBD-Cog (n = 15)	CBD-CBS (n = 31)	p Value
Clinical features			
Female, n (%)	7/8 (47)	14/17 (45)	
Age at death, y	70 (61, 73)	70 (68, 75)	
Age at onset, y	63 (55, 68)	64 (60, 69)	
Duration, y	6.0 (5.0, 7.5)	6.5 (5.0, 8.0)	
Pathologic features			
Brain weight, g	1,040 (940, 1,080)	1,100 (980, 1,200)	0.027
Braak neurofibrillary tangle stage	II (I–II, II–III)	II–III (II, III)	
Thal Aβ phase	0 (0, 1)	0 (0, 1)	
AGD, n (%)	11 (73)	11 (35)	0.036
Amygdala TDP-43, n (%)	7 (45)	10 (34)	
Amygdala α-synuclein, n (%)	0 (0)	0 (0)	
Alzheimer type neurofibrillary tangles (thioflavin S fluorescent microscopy)			
Middle frontal	0 (0, 0)	0 (0, 0)	
Superior temporal	0 (0, 0)	0 (0, 0)	
Inferior parietal	0 (0, 0)	0 (0, 0)	
Endplate	0 (0, 0)	0 (0, 1)	
CA2/3	0 (0, 1)	1 (0, 2)	
CA1	0 (0, 1)	1 (0, 2)	
Subiculum	1 (0, 2)	1 (0, 2)	

Abbreviations: Aβ = β-amyloid; AGD = argyrophilic grain disease.

CBD-Cog was matched to CBD-CBS for age, sex, and disease duration. Participants are also matched for Alzheimer type summary measures (Braak neurofibrillary tangle stage and Thal amyloid phase), which were uniformly low in both groups. Counts of neurofibrillary tangles in neocortex and hippocampal subfields based upon thioflavin S fluorescent microscopy were also uniformly low in both groups. Cases were not matched for brain weight, AGD, or TDP-43 pathology. Brain weight was less in CBD-Cog and AGD was more frequent in CBD-Cog. All variables were analyzed with Kruskal-Wallis analysis of variance on ranks and data are displayed as median (25th percentile, 75th percentile) or percent of patients with the specific feature, unless otherwise noted. Only significant p values (p < 0.05) are indicated.

preservative, stereotyped, or compulsive/ritualistic behavior, and (5) hyperorality and dietary changes. We used the Armstrong criteria³ for the clinical diagnosis of CBS, and all patients included in the study met criteria for CBS (24 probable and 7 possible). One psychologist (O.A.S.) and one neurologist (N.S.) reviewed all cognitive assessments.

Genetic analyses

Genotyping was performed with TaqMan allelic discrimination assay on an ABI 7900HT fast real-time PCR system (Applied Biosystems, Foster City, CA). One single nucleotide polymorphism (SNP) (rs1052553) was used to determine *MAPT* haplotype and 2 SNPs (rs7412 and rs429358) were used to determine *APOE* genotype.

Microscopic pathology

All cases had standardized processing and were evaluated by a single neuropathologist (D.W.D.). Gross and macroscopic neuropathologic assessment was performed by standardized procedures. Formalin-fixed, paraffin-embedded tissue samples were cut at 5 μ m thickness and mounted on glass slides for further study. In addition to histologic evaluation, presence and severity of Alzheimer pathology was assessed with thioflavin-S fluorescent microscopy. A Braak NFT stage¹¹ and Thal amyloid phase¹² were assigned based upon lesion counts in cortical and subcortical areas with thioflavin S fluorescent microscopy.

Immunohistochemistry

Immunohistochemistry was performed on 5- μ m-thick sections of formalin-fixed, paraffin-embedded tissue. Glass-mounted sections were deparaffinized in xylene and rehydrated in ethanol and distilled water. Immunohistochemistry for tau used an antibody to phospho-serine 202 (CP13, mouse monoclonal; from Peter Davies, PhD, Feinstein Institute, North Shore Hospital, NY). Nine sections, which covered almost all major anatomical regions affected in CBD, were processed for immunohistochemistry for phospho-TDP-43 (pS409/410, mouse monoclonal, 1:5,000; Cosmo Bio, Tokyo, Japan) according to previously published methods.²¹

All immunohistochemistry was performed using a DAKO AutostainerPlus (Agilent/DAKO, Santa Clara, CA) with the DAKO EnVision + system-HRP with 3,3'-diaminobenzidine (DAB) as the chromogen. Nonspecific antibody binding was blocked with normal goat serum (Sigma, St. Louis, MO).

Image analysis

Digital microscopy methods have been described previously.²² Briefly, immunostained sections were scanned on an Aperio ScanScope XT slide scanner (Aperio Technologies, Vista, CA), producing a high-resolution digital image. Digital image analysis was performed using Aperio ImageScope software. Several regions of interest were outlined from each image. A color deconvolution algorithm was used to count the number of pixels that were strongly immunostained by the

DAB chromogen in outlines of the region of interest. The output variable was percentage of strong positive pixels relative to the total area of the region of interest.

Statistical analysis

Sigma Plot Version 12 (Systat Software, San Jose, CA) was used for statistical analyses. Due to the small sample sizes, nonparametric Kruskal-Wallis analysis of variance on ranks was performed on quantitative measures to assess differences in the median values. Post hoc pairwise comparisons were performed between each of the groups using Mann-Whitney rank sum test. For categorical data (e.g., sex and *APOE* genotype, clinical symptoms), a χ^2 test was used to compare group differences. Fisher exact test was used for comparison of pairwise categorical data if the counts were less than 5. Correlative analysis was performed using Spearman rank order correlation. A statistically significant difference was considered for 2-sided $p < 0.05$.

Data availability

This clinicopathologic study is not a clinical trial; therefore, the requirements of International Committee of Medical Journal Editors are not applicable. Nevertheless, deidentified clinical information and summary statistics, as well as neuropathology data, are available according to the policies of *Neurology*[®]. There are no specific exceptions regarding data availability.

Results

Demographics and pathologic findings

Among 217 autopsy-proven CBD cases in the Mayo Clinic brain bank from 1998 to 2018, we identified 18 patients with antemortem clinical diagnoses of amnesic dementia, without motor symptoms or motor symptom only developing later in the disease course. We excluded cases with significant AD neuropathologic change, hippocampal sclerosis,¹⁶ severe cerebrovascular pathology, or cortical Lewy bodies (table e-1, doi.org/10.5061/dryad.1vhhmqp5). Five CBD-AD cases were included in this study. We identified 10 cases meeting clinical criteria for FTD and after applying the same exclusion criteria. We identified 31 CBD-CBS cases with similar demographic features and pathologic exclusion criteria to CBD-Cog (table 1). The 15 CBD-Cog cases included 8 men and 7 women; CBD-CBS cases included 17 men and 14 women. The mean age at death, age at onset, and disease duration did not differ between CBD-Cog and CBD-CBS. The 2 groups did not differ with respect to Alzheimer-type pathology as assessed with Braak NFT stage and Thal amyloid phase, but they did differ with respect to brain weight (less in CBD-Cog) and frequency of AGD (more in CBD-Cog) (table 1).

Initial clinical features

Initial signs and symptoms of CBD-Cog and CBD-CBS are summarized in table 2. At initial presentation, 1 patient with CBD-Cog and 8 patients with CBD-CBS had balance

Table 2 Initial signs and symptoms of cognitive predominant corticobasal degeneration (CBD-Cog) and corticobasal degeneration with corticobasal syndrome (CBD-CBS)

	CBD-Cog (n = 15), n (%)	CBD-CBS (n = 31), n (%)	p Value
Motor features			
Gait disorder/ falls	1 (7)	8 (26)	NS
Limb dysfunction	0 (0)	22 (80)	<0.001
Cognitive impairment			
Personality/ behavior	6 (40)	0 (0)	<0.001
Aphasia	5 (33)	3 (20)	NS
Memory	5 (33)	0 (0)	0.002

Data are displayed as frequency of a given clinical feature (percent of total in that group). Post hoc pairwise comparison analysis is performed with Mann-Whitney rank sum test. Only statistically significant *p* values are shown.

problems or falls. Limb dysfunction was noted in 80% of patients with CBD-CBS, but in none of the patients with CBD-Cog. By definition, all patients with CBD-Cog presented with cognitive symptoms. As the initial symptom, speech problems, but not dysphasia, were noted in 5 patients (33%), behavioral changes were noted in 6 patients (40%), and subjective memory problems were noted in 5 patients (33%) with CBD-Cog.

Clinical features during the disease course

Table 3 summarizes a comparison of clinical features during the disease course for CBD-Cog and CBD-CBS. Given that the groups were included if they fit accepted clinical criteria for CBD-CBS and CBD-Cog, the majority of differences between the 2 groups were expected, such as limb apraxia being significantly more frequent in CBD-CBS and behavioral problems being significantly more frequent in CBD-Cog. There were several notable findings. In particular, disinhibition, subjective memory complaints, and language difficulties were not significantly different between CBD-Cog and CBD-CBS, although all tended to be higher in CBD-Cog than in CBD-CBS.

Cognitive assessment

Compared to the 24 CBD-CBS cases with detailed cognitive testing, the 15 CBD-Cog cases demonstrated significantly more executive dysfunction and, although not significant, greater visuospatial problems. Interestingly, both CBD-Cog and CBD-CBS cases had no or minimal problems with naming or long-delay cued memory recognition (table 3).

Pathologic findings

Representative macroscopic images of a patient (Case 11) with CBD-Cog are shown in figure 1. The distribution of

cerebral atrophy was not limited to parasagittal and perirolandic area, which is often the case in CBD-CBS. Superior, middle, and inferior (opercular) frontal gyri and superior gyrus were also atrophic (figure 1A). Lateral ventricle enlargement affected both frontal and temporal horns (figure 1B). The temporal horns are not usually enlarged in CBD. In contrast to most cases of CBD, neuromelanin pigmentation of substantia nigra was preserved (figure 1C).

To investigate difference in tau distribution and density, we performed immunohistochemistry for phospho-tau in CBD-Cog and CBD-CBS (figure 2) followed by digital image analysis to quantify the density of phospho-tau burden in regions of interest. CBD-Cog had significantly greater tau burden in both gray and white matter of the inferior temporal gyrus and the superior gyrus compared with CBD-CBS (table 4). In contrast, CBD-CBS had greater tau burden in gray and white matter of motor cortex compared with CBD-Cog.

Assessment of tau burden in medial temporal lobe structures revealed significantly more tau in CBD-Cog in the hippocampus proper, parahippocampal gyrus, and amygdala compared with CBD-CBS. On the other hand, the tau burden was significantly less in both gray and white matter in the motor cortex in CBD-Cog compared with CBD-CBS (table 4). These results suggested that tau density and distribution might be associated with cognitive impairment in CBD-Cog and motor problems in CBD-CBS. Although our digital image analysis suggested that total density and distribution of tau pathology may be associated with clinical phenotype, the total tau burden does not distinguish the contribution of various tau pathologies (neuronal perikaryal pathology, tau threads, astrocytic plaques, and coiled bodies) to the total burden score. Therefore, we also investigated the role of different cellular tau pathologies using a semiquantitative assessment of neuronal and glial lesions, as well as tau threads, which may originate from both neurons and glia (table 4).

Semiquantitative tau lesion scores

Semiquantitative analysis of tau lesions is summarized in table 4. Intraneuronal tau pathology included lesions that resembled NFT, as well as pretangles. There were no significant differences between CBD-Cog and CBD-CBS in superior frontal cortex, but CBD-Cog had significantly more neuronal lesions in the temporal cortex and significantly fewer neuronal lesions in the motor cortex. Abundant tau threads in both gray and white matter is a characteristic neuropathologic feature of CBD.³ CBD-Cog had significant greater tau threads in temporal cortex compared with CBD-CBS (*p* < 0.001). Astrocytic plaques are the histopathologic hallmark of CBD,³ while oligodendroglial coiled bodies can be detected in a number of tauopathies including progressive supranuclear palsy and AGD, in addition to CBD. There were no differences between CBD-Cog and CBD-CBS for astrocytic plaque scores in any of the regions studied (not shown). Scores for oligodendroglial coiled bodies were greater in inferior temporal white

Table 3 Clinical features during the disease course of cognitive predominant corticobasal degeneration (CBD-Cog) and corticobasal degeneration with corticobasal syndrome (CBD-CBS)

	CBD-Cog (n = 15), n (%)	CBD-CBS (n = 31), n (%)	p Value
Motor features			
Parkinsonism	6 (40)	31 (100)	<0.001
Gait	3 (40)	26 (84)	<0.001
Dystonia	1 (7)	14 (45)	0.017
Cognitive impairment			
Behavior	14 (93)	6 (19)	<0.001
Apathy	8 (53)	5 (16)	0.014
Disinhibition	4 (27)	1 (3)	
Memory (subjective)	5 (30)	5 (16)	
Language (primary progressive aphasia)	7 (47)	8 (26)	
Apraxia	4 (27)	24 (77)	0.003
Cognitive tests			
Executive dysfunction	12/15 (80)	10/24 (43)	0.04
Visuospatial abnormality	7/15 (47)	6/24 (25)	
Language (naming) deficit	1/15 (7)	0/24 (0)	
Memory (long delay cued recall) deficit	0/15 (0)	0/24 (0)	

Data are displayed as frequency of given clinical feature (percent of total in that group). Post hoc pairwise comparison analysis was performed with Mann-Whitney rank sum test. Only statistically significant *p* values are shown. Only statistically significant *p* values are shown.

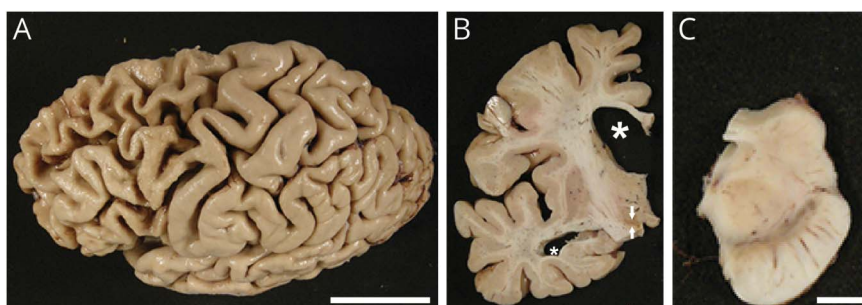
matter in CBD-Cog, but significantly less in white matter beneath the motor cortex.

Discussion

CBD is a rare, progressive neurodegenerative disorder with a range of clinical presentations depending upon the degree and distribution of neocortical pathology.²³ The heterogeneous combination of motor, sensory, behavioral, and cognitive symptoms makes antemortem diagnosis difficult, and at

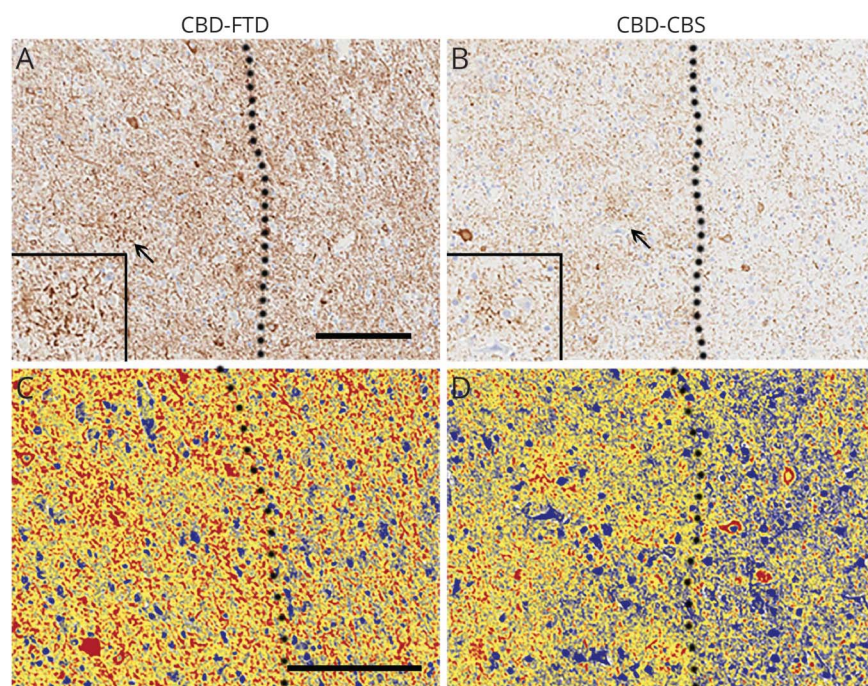
autopsy a correct diagnosis is no greater than 50% in the Cure PSP Brain bank at Mayo Clinic (personal observations) and in the Queen Square Brain Bank.⁶ Although cognitive deficits are common in CBD, it is not widely recognized that some patients may initially present with predominantly cognitive dysfunction with minimal or no motor findings,⁹ here termed CBD-Cog. A subset eventually develops motor signs, but some do not. The neuropathologic features of CBD-Cog have not been studied previously. Therefore, we aimed to characterize clinical and pathologic characteristics of this uncommon presentation of CBD. In an initial screen, we

Figure 1 Representative macroscopic findings in cognitive predominant corticobasal degeneration (CBD-Cog)



An example of macroscopic findings in CBD-Cog. (A) Marked frontal and temporal cortical atrophy. (B) Enlargement of the frontal and temporal horns of the lateral ventricle (*). (C) Minimal pigment loss in substantia nigra. Scale bars in A and C, respectively: 4 cm, 0.5 cm.

Figure 2 Phospho-tau immunohistochemistry in cognitive predominant corticobasal degeneration (CBD-Cog) and corticobasal degeneration with corticobasal syndrome (CBD-CBS)



Representative high magnification images of superior frontal gyrus immunostained for phospho-tau in CBD-Cog (A) and CBD-CBS (B). Scale bar: 200 μ m. Application of digital imaging mask in CBD-Cog (C) and CBD-CBS (D) in order to analyze tau burden with a color deconvolution algorithm. Strong positive pixels are in red. A positive pixel count algorithm was customized to quantify brown immunoreactive pixels (red markup), subtracting inverse (blue) and background pixels (yellow). Tau burden is the ratio of strong positive pixels to all pixels in the region of interest. The analysis does not discriminate among neurofibrillary tangles, tau threads, coiled bodies, or astrocytic tau pathology. Left side of dashed line shows cortical gray matter and right side of dashed line shows white matter. Scale bar: 150 μ m.

identified 13 patients with CBD with a final clinical diagnosis of bvFTD, and 10 were included in the analysis after exclusion of comorbid pathologic processes and requirement for high-quality medical documentation. We also identified 18 patients with CBD who were thought to have AD as a final clinical assessment; only 5 met rigorous inclusion and exclusion criteria. We excluded cases with intermediate to high likelihood AD,¹⁵ significant cerebrovascular pathology, cortical Lewy bodies, or hippocampal sclerosis. The initial symptom in all 5 CBD-AD cases was memory loss. Patients with CBD-FTD were more heterogeneous, with 4 presenting with personality or behavioral changes, 2 with language and behavioral problems, 3 with language problems, and 1 with executive dysfunction. In this group, 5 patients never had apparent motor problems during the disease course, even at late stages of the disease. An asymmetrical motor problem was recorded in only 4 CBD-Cog patients at end stage disease (table e-2, doi.org/10.5061/dryad.1vhhmgqp5). CBD presenting with symmetric motor deficits is increasingly recognized and often misdiagnosed during life. Hassan et al.²⁴ described 5 (out of 31) patients with autopsy-confirmed CBD and a symmetrical motor phenotype.

The nature of the cognitive dysfunction in CBD-Cog was heterogeneous, including language deficits, visuospatial and executive dysfunctions, apraxia, and behavioral disorders (table e-2, doi.org/10.5061/dryad.1vhhmgqp5). While apraxia and early limb dysfunction were significantly more common in CBD-CBS, early memory and personality

changes, as well as apathy and behavioral changes, were more common in CBD-Cog (tables 2 and 3). Interestingly, although not autopsy-proven, Moretti et al.²⁵ reported that apathy is a predominant feature of behavioral impairment in probable CBD; it was noted as an isolated symptom in nearly 70% of patients as an initial complaint. In a focused review of all available neuropsychiatric evaluations and cognitive tests in our patients with CBD-Cog, we noted that objective evidence of memory loss in standardized tests or screening instruments was not common, but patients with CBD-Cog frequently had subjective memory complaints associated with executive dysfunction. Our findings in CBD-Cog are consistent with previous cognitive characterization of CBD. Patients have executive dysfunction, visuospatial dysfunction, behavioral change, and preserved semantic and episodic memory. In our cohort, executive dysfunction and apathy were key clinical features of CBD-Cog.

There are several published clinicopathologic studies that are relevant to CBD-Cog. Kertesz et al.²⁶ reported on a prospectively studied cohort of 32 patients with bvFTD, which at autopsy included 4 patients with CBD, and 22 patients with primary progressive aphasia, which at autopsy included 5 patients with CBD. In a retrospective autopsy series, Grimes et al.⁹ reported only 4 of 13 patients with CBD had antemortem clinical features of CBS. Six were thought to have AD, 1 had AD and parkinsonism, and 2 had frontotemporal dementia.⁹ They concluded that dementia may be the most common presentation of CBD. Forman et al.¹⁰ reported 12

Table 4 Tau pathology in cognitive predominant corticobasal degeneration (CBD-Cog) and corticobasal degeneration with corticobasal syndrome (CBD-CBS)

	CBD-Cog (n = 15)	CBD-CBS (n = 31)	p Value
Phospho-tau pathology from image analysis			
Superior frontal cortex	8.7 (3.5, 11.2)	4.1 (3.0, 6.6)	0.044
Superior frontal cortex white matter	7.6 (6.2, 12.9)	3.1 (1.8, 5.7)	0.004
Temporal cortex	1.7 (1.2, 3.6)	0.6 (0.3, 1.3)	0.002
Temporal cortex white matter	1.4 (0.6, 1.7)	0.3 (0.1, 0.7)	0.008
Motor cortex	5.7 (2.0, 7.4)	10.1 (7.5, 15)	<0.001
Motor cortex white matter	0.9 (0.6, 2.3)	5.3 (3.2, 8.9)	<0.001
Hippocampus	5.3 (3.5, 9.8)	2.1 (1.0, 4.4)	<0.001
Parahippocampal gyrus	1.6 (1.0, 4.6)	0.8 (0.3, 1.6)	0.026
Amygdala	8.8 (5.3, 15)	2.7 (1.2, 5.5)	<0.001
Tau pathology from semiquantitative scores			
Superior frontal cortex neuronal tau	3 (3, 3)	3 (3, 3)	
Superior frontal cortex tau threads	3 (3, 3)	3 (3, 3)	
Superior frontal cortex white matter coiled bodies	2 (2, 3)	2 (1, 2)	
Inferior temporal cortex neuronal tau	3 (3, 3)	2 (2, 3)	0.012
Inferior temporal cortex tau threads	3 (2, 3)	2 (1, 2)	<0.001
Inferior temporal cortex white matter coiled bodies	2 (1, 2)	1 (1, 2)	0.039
Motor cortex neuronal tau	3 (2, 3)	3 (3, 3)	0.025
Motor cortex tau threads	3 (2, 3)	3 (3, 3)	
Motor cortex white matter coiled bodies	1 (1, 1)	2 (2, 3)	<0.001
Hypothalamus tau threads	2 (2, 3)	2 (1, 2)	0.001
Caudate nucleus coiled bodies	2 (1, 2)	1 (1, 2)	0.049

Tau pathology measures, including those from image analysis and from semiquantitative scoring of tau lesions. All variables are analyzed with Kruskal-Wallis analysis of variance on ranks, and data are displayed as median (25th and 75th range). Post hoc pairwise comparison analysis is performed with Mann-Whitney rank sum test. Only statistically significant *p* values are shown.

autopsy-confirmed cases of CBD, 2 with antemortem clinical diagnoses of AD and 2 with bvFTD; only 50% had CBS. Lee et al.²⁷ reported that in 18 autopsy-confirmed CBD cases, 5 presented as bvFTD and 5 presented as PNFA, but none was thought to have AD. Josephs et al.²⁸ reported 17 cases with progressive aphasia and apraxia of speech, of which 5 had CBD. In addition, of 21 patients with CBD reported by Josephs et al.,²⁹ 2 had presented with bvFTD.

In a multicenter study, Armstrong et al.¹ reviewed the initial diagnosis of autopsy-confirmed cases of CBD (which included data from Mayo Clinic brain bank series). CBS was the most common presenting syndrome (27%, 35/129), followed by FTD (16%, 20/129), Parkinson disease or atypical Parkinson disease (16%, 20/129), and primary progressive aphasia (15%, 19/129). Of note, 9% of CBD cases had an antemortem clinical syndrome of AD type dementia

(2/129).³ Day et al.³⁰ reported that CBD may mimic AD early in the disease course in a comparative analysis of autopsy-confirmed CBD (n = 17) and AD (n = 16). They noted that patients with CBD had declines in episodic memory, executive functioning, and letter fluency. The reported proportion of CBD-Cog in autopsy series is variable, but it is clearly less than half of all CBD cases.

Few studies have addressed the neuropathologic features of CBD-Cog. Grimes et al.⁹ suggested that greater frontal cortical tau pathology was a correlate of CBD presenting with dementia. In the present study, superior frontal and inferior temporal cortical tau pathology was greater, while motor cortex tau pathology was less in CBD-Cog compared with CBD-CBS. This was true for both gray and white matter. The cellular pathology that was most associated with CBD-Cog was not astrocytic, but rather neuronal and oligodendroglial. Tau

threads in both gray and white matter were also significant. Our results provide evidence that not only total tau burden, but also pathology of specific cellular types (neuronal and oligodendroglial) are associated with cognitive dysfunction.

An unexpected finding was the increased frequency of AGD in CBD-Cog (73%) compared with CBD-CBS (35%). We aimed to match CBD-CBS with CBD-Cog by demographic and comorbid pathologies associated with dementia (e.g., Alzheimer type pathology, cerebrovascular pathology, and cortical Lewy bodies), but we did not match for frequency of AGD. In a previous study we found that about 40% of CBD cases have AGD,¹³ but we did not associate this observation with a particular clinical phenotype. The frequency was even higher in the present autopsy cohort (47%), and our clinicopathologic findings study suggests that it may be associated with CBD-Cog. AGD is a 4-repeat tauopathy that increases in frequency with age.^{14,31,32} In a study of 2,661 postmortem brains, Braak found 125 cases with AGD (5%), and that the frequency of AGD increased with age from 5% for cases under 60 years of age to over 10% for those older than 70 years.¹⁴ The frequency in the oldest old (100 years or older) may be as high as 31%.³³ Given the predilection of AGD to the medial temporal lobe, we were concerned that it might account for the higher temporal lobe tau pathology in CBD-Cog. Multiple regression modeling suggests that this is not the case (table e-4, doi.org/10.5061/dryad.1vhhmgqp5). The clinical significance and correlates of AGD are uncertain. It rarely occurs as an isolated disease process. Nevertheless, it is thought to be associated with mild cognitive impairment,³⁴ late-onset psychosis,³⁵ bipolar disorder, and depression.³⁶ Further studies are needed to confirm the association of AGD with cognitive dysfunction in CBD.

It is challenging to differentiate patients with CBD-Cog from those with AD and FTD, but improvement in antemortem biomarkers holds promise that this may eventually be solved. Use of biofluid biomarkers, including β -amyloid and phospho-tau,³⁷ may rule out AD in patients with CBD-AD, but they will remain problematic in cases of CBD with mixed Alzheimer type pathology, which increases in frequency with age. Structural, functional, and molecular (e.g., amyloid PET) neuroimaging studies suffer from the same problems as biofluid biomarkers. Development of tau PET that is specific for 4-repeat would theoretically be a better way to distinguish CBD-AD from AD. Both Josephs et al.³⁸ and McMillan et al.³⁹ reported that ¹⁸F-AV1451 tau PET correlated with 4-repeat tau burden in autopsy-confirmed CBD.

This study has strengths and limitations. Given that only 15 cases of CBD met the final exclusion criteria, one might question the representativeness of the cohort. Clearly, this autopsy cohort is a sample of convenience, albeit the largest such convenience sample in the world with standardized neuropathologic evaluation. The largest number of cases excluded in this study was the group of pathologically confirmed CBD with an antemortem clinical syndrome of progressive

supranuclear palsy (i.e., Richardson syndrome⁴⁰) (n = 89, 41%). While Richardson syndrome is associated with subcortical executive dysfunction,⁴¹ it is primarily a motor rather than a cognitive disorder, justifying its exclusion from this more focused study. The patients with CBD included in this study were derived from a referral brain bank and are not population-based; therefore a selection bias, particularly for atypical presentations,⁴² is possible. Another weakness is that medical documentation was not uniform or standardized; however, cases were included only if they had good clinical documentation and the patients were seen by a neurologist or neuropsychologist. A limitation is the variable length of time from clinical or neuropsychologic evaluation to death. A strength of the study is that all cases were referred to a single brain bank, so neuropathologic procedures were systematic and standardized, including semiquantitative and digital pathology analyses. In addition, given the large number of CBD cases in the brain bank with CBS, we were able to match CBD-Cog to CBD-CBS on a number of clinical, demographic, and pathologic measures, making it more likely that observed differences are biologically relevant to cognitive deficits.

We studied patients with CBD presenting with cognitive predominant syndromes resembling AD or bvFTD and clinical and pathologic measures that differed from typical CBD-CBS. We found prominent executive dysfunction, language problems, visuospatial problems, and apathy as characteristic features of CBD-Cog. Neuropathologic features of CBD-Cog were greater frequency of AGD, as well as greater tau pathology in frontal and temporal cortices and less tau pathology in motor cortex. While astrocytic plaques are the histopathologic hallmark of CBD, the number and distribution of astrocytic plaques did not correlate with clinical syndrome, but neuronal tau, tau treads, and oligodendroglial tau did. Our study suggests that CBD should be in the differential diagnosis of patients who present with dementia and executive dysfunction, especially apathy, even if they do not have overt extrapyramidal or motor features.

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Octavio A. Santos, PhD	Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data, revised the manuscript for intellectual content
Otto Pedraza, PhD	Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data, revised the manuscript for intellectual content
Irene Litvan, MD	Department of Neurology, University of California San Diego, La Jolla	Revised the manuscript for intellectual content
Melissa E. Murray, PhD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Major role in the acquisition of data, revised the manuscript for intellectual content
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Ryan J. Uitti, MD	Department of Neurology, Mayo Clinic, Jacksonville, FL	Revised the manuscript for intellectual content
Zbigniew K. Wszolek, MD	Department of Neurology, Mayo Clinic, Jacksonville, FL	Revised the manuscript for intellectual content
Neill R. Graff-Radford, MBBS	Department of Neurology, Mayo Clinic, Jacksonville, FL	Revised the manuscript for intellectual content
Keith A. Josephs, MD, MST, MSc	Department of Neurology, Mayo Clinic, Jacksonville, FL	Revised the manuscript for intellectual content
Dennis W. Dickson, MD	Department of Neuroscience, Mayo Clinic, Jacksonville, FL	Designed and conceptualized study, major role in the acquisition of data, analyzed the data, revised the manuscript for intellectual content

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