

Is the Pathology of Corticobasal Syndrome Predictable in Life?

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Abstract: Corticobasal syndrome (CBS) has been associated with a heterogeneous spectrum of pathologies with an increasing number of reports of Alzheimer's type pathology. There is, however, no means of predicting pathology of CBS in vivo at present. We compared the clinical features of patients presenting with CBS who have either pathologic changes of classic corticobasal degeneration (CBD) or Alzheimer's disease (AD) at post-mortem to identify predictors of the specific pathological processes in life. Twelve patients with CBS were followed prospectively; six had AD and six had classic CBD neuropathology. After review of the presenting clinical features, we identified nine potential predictor variables, compared their frequency in the two groups, and performed a discriminant function analysis. Initial epi-

sodic memory complaints and poor performance on the combined orientation-memory subtest of the Addenbrooke's Cognitive Examination (ACE) reliably predicted AD pathology while varying combinations of early frontal-lobe type behavioral symptoms, nonfluent language disturbance, orobuccal apraxia, and utilization behavior predicted CBD pathology ante-mortem. CBS is frequently associated with Alzheimer's disease pathology. Early episodic memory impairment versus early behavioral symptomatology appears to best predict AD or CBD pathology in life. © 2009 Movement Disorder Society

Key words: corticobasal syndrome; corticobasal degeneration; Alzheimer's disease; pathology; behavior; nonfluent aphasia; utilization behavior

INTRODUCTION

The syndrome of Corticobasal Degeneration (CBD) is of considerable interest to movement disorder specialists and behavioral neurologists. Although initially described as a distinctive levodopa-resistant, asymmetric, akinetic-rigid syndrome associated with prominent apraxia, cortical sensory loss, focal reflex myoclonus, and alien limb phenomena,¹ it has become increasingly clear that cognitive and behavioral features are also extremely common with considerable overlap between CBD, progressive supranuclear palsy (PSP), and frontotemporal dementia (FTD) syndromes.^{2–4}

As originally conceived, CBD was also considered a distinct pathologic disorder characterized by cortical degeneration with swollen 'achromatic' neurons, neuronal loss in the substantia nigra and extensive neuronal and glial cytoplasmic tau-positive inclusions. More recently, however, there is growing evidence that patients with clinically classic CBD have alternative pathologies^{5–12} including AD, PSP, and FTD leading some investigators to propose the label of Corticobasal Syndrome (CBS).^{13–15} Recent advances in molecular and genetic research have shown that mutations, mutations of the *microtubule associated protein tau* (*MAPt*) and *progranulin* gene in association with ubiquitinated neuronal cytoplasmic inclusions occur in CBD with FTD.^{16,17}

It is unclear from the current literature, however, whether there are any systematic differences between patients with and without corticobasal degeneration pathology. A very recent clinico-pathological study of patients with classic tau inclusion CBD emphasized early language dysfunction, executive and socio-behavioral

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changes, and the relative preservation of episodic memory.¹⁸ We reviewed our series of 12 clinically-diagnosed and prospectively-assessed patients with CBS that came to post mortem. Six had pathologically-confirmed classic CBD while the remaining six cases had AD pathology. The primary aim of this study was to investigate whether any clinical predictor variables could identify which specific pathology caused the CBS ante-mortem.

SUBJECTS AND METHODS

Case Selection

Twelve consecutive cases diagnosed clinically with CBS between 1997 and 2004 were followed up at regular intervals in the Disorders of Movement and Cognition Clinic. All patients underwent neurological examination, neuroimaging studies that (structural and functional) and standard neuropsychological assessments, including the Addenbrooke's Cognitive Examination (ACE)¹⁹ and were prospectively followed up until death every 6 months.

Since the establishment of the DMC every effort was made to follow-up any patient with CBS and to enrol them into the Brain Bank. All patients were referred by other consultant neurologists with a putative diagnosis of CBS. After review of the database, we found only three other cases who were lost to follow-up. The 12 reported here represent therefore the majority (12 of 15) of those seen over a 7-year period.

Data Collection

All 12 patients fulfilled the diagnostic criteria for CBS and had been assessed by one of the two behavioral neurologists (JRH and THB). The following essential core diagnostic criteria were used: (1) asymmetrical presentation, (2) akinetic-rigid syndrome, (3) ideomotor apraxia, and (4) signs of frontal-executive dysfunction. Apraxia was systematically assessed by asking subjects to first copy a series of meaningless gestures, then to mime to command meaningful gestures and finally to copy the examiner performing transitive movements.²⁰ The supportive criteria included (1) insidious onset and gradual progression (2) lack of sustained response to dopaminergic treatment (3) myoclonus, (4) dystonia, (5) alien hand syndrome, (6) cortical sensory loss tested by two-point discrimination, graphaesthesia or tactile object recognition, (7) visuospatial deficits, and (8) progressive nonfluent aphasia.²⁰ The diagnosis of CBS was based on the presence of at least three essential and four supportive features.

The medical records, clinical and neuroimaging information were reviewed by a behavioral neurologist (BPS) blind to the neuropathology results. Particular attention was paid to the first clinical assessment, date of diagnosis, and onset of first symptom as reported by the family. "Early" features were defined as clinical symptoms apparent during the initial third of the disease duration, "Late" as features that represented the patient's state towards the end of disease progression, and "Mid" as features that were evident in the mid-phase of the disease process.

Neuropathology

All 12 cases had undergone neuropathological examination by the same senior neuropathologist (JHX) without access to clinical information other than age and date of death. The routine procedure for brain collection and preparation is discussed elsewhere.²¹ In brief, the cerebral hemispheres were bisected and the left cerebral hemisphere and attached half of the mid-brain was fixed in 10% buffered formalin while the right cerebral hemisphere, right hemi-brainstem and the left cerebellar hemisphere were snap frozen.

Tissue blocks were taken from the frontal (Brodmann area 6/46), temporal (area 21/ 22), parietal (area 39/40), occipital (area 17/18), and anterior cingulate (area 24) cortex, as well as from anterior medial temporal lobe, posterior medial temporal lobe, midbrain (substantia nigra), pons, medulla oblongata (hypoglossal nucleus), and cerebellum.

Sections from all regions were stained with haematoxylin, eosin and immunohistochemical techniques for the assessment of neurodegenerative changes using current diagnostic protocols.²²⁻²⁵ In addition to the application of Braak staging for Alzheimer-type pathology,²⁶ other specific lesions sought were Pick bodies, Pick cells, glial tau pathology, cytoplasmic ubiquitin-positive tau-negative inclusions, intranuclear ubiquitin inclusions, ubiquitinated neurites, neurofilament inclusions, Lewy bodies, and β A4 peptide deposition in the neuropil and in blood vessels.

Each case was placed in a diagnostic category based on the occurrence of specific microscopic lesions. A diagnosis of Alzheimer's disease (AD) was made in six cases on the basis of Braak Stage 4 or greater pathology²⁶ which required the presence of both neuritic plaques and neurofibrillary tangles, with the involvement of isocortex. The remaining six patients displayed ballooned neurons, tau-positive neuronal and glial inclusions, threads and grains, and nigral degeneration that were consistent with the standard criteria for the diagnosis of CBD.²⁴

Statistical Analysis

Demographic variables were analyzed with unpaired students' *t*-tests. Non-parametric statistics (Mann-Whitney *U* tests) were used for analysis of median survival times from onset and presentation.

On the basis of review of the literature, and our clinical experience, we identified nine potential variables that might predict AD or CBD pathology ante-mortem, and compared the frequency in both groups. These nine clinical variables were (1) initial episodic memory complaints, (2) early visuospatial features, (3) prominent nonfluent language impairment, such as distorted articulation and /or phonological errors in speech (4) frontal-lobe type behavioral alterations, such as personality changes, disinhibition, apathy, emotional blunting and loss of insight (5) recent change in eating behavior, (6) presence of utilization behavior, (7) oculomotor apraxia, (8) orobuccal apraxia, and (9) the combined orientation-memory subtests from the ACE. We hypothesized that initial episodic memory complaints and the ACE-OM combined subtest scores would best discriminate AD from CBD, while the other variables would be predictors of CBD pathology.

Dichotomous clinical variables indicating the presence or absence of individual features were analyzed to calculate Likelihood Ratios (SPSS 12.0.1, Apache Software Foundation). Statistical significance was set at a threshold of 0.01.

For the purpose of this analysis, a feature was regarded as *present* if it appeared at any stage in the clinical course. Follow-up discriminant analysis was done to identify the most important variables contributing to group separation.

RESULTS

Table 1 summarizes the demographic, cognitive, and survival data. The male to female ratio was 2:4 in AD and 4:2 in the CBD group. At presentation patients with CBD were comparatively younger than the AD group by about 4 years; but this difference was not significant, ($t(10) = 1.24, P = 0.20$). In the CBS-AD group, median survival time from symptom onset was 12 years (SD 4.5; range: 5–13], and 8 years from diagnosis (SD 4.3; range: 1–11]. These indices were shorter in the classic CBD group: median survival times from onset and diagnosis were 5 years (SD 2.8; range, 4–11] and 3.5 years (SD 2.1; range, 3–8] years, respectively. Although, the disease duration of CBD was ~ 7 years shorter than in the AD group, the difference was not significant, ($t(10) = 1.24, P = 0.24$). There was no

TABLE 1. Summary of demographic and cognitive data

	AD		CBD		<i>P</i>
	Mean	SD	Mean	SD	
Demographic features					
Age at symptom onset (yr)	69.5	5.1	65.8	5.1	0.24 (ns)
Time to presentation	3.5	1.4	2.5	1.4	0.24 (ns)
Survival from symptom onset ^a	12	4.5	5	2.8	0.24 (ns)
Survival from diagnosis ^a	8	4.3	3.5	2.8	0.49 (ns)
Cognitive scores					
MMSE (n = 12)	18.0	4.2	22.7	3.4	<0.05
ACE (n = 10)	46.8	4.1	73.4	8.5	<0.001
Orientation	5.4	2.7	9.0	1.2	<0.05
Memory	15.2	6.1	28.4	4.3	<0.01
O-M total	20.6	8.2	37.4	5.0	<0.01

^aMedian survival in years.

SD, standard deviation; ns, not significant; MMSE, mini mental state examination; ACE, Addenbrooke's cognitive examination; O-M total, Combined orientation and memory subscore of the ACE.

family history of dementia and/or movement disorder in any of the patients in our series.

The clinical details of each patient are summarized in Table 2. Six features were distributed significantly differently across the groups. Four features, namely frontal type behavioral symptoms (LR = 10.9, $P < 0.001$), initial nonfluent language impairment (LR = 7.6, $P < 0.01$), utilization behavior (LR = 7.6, $P < 0.01$) and orobuccal apraxia (LR 7.6, $P < 0.01$) were more frequent in the CBD group, whereas two features: initial episodic memory complaints (LR = 10.9, $P < 0.001$) and the ACE combined orientation-memory subscore (LR = 10.9, $P < 0.001$) were more commonly represented in the AD group. Alterations in eating behavior, early abnormalities of visuospatial function, and oculomotor apraxia were not distributed differently across the subgroups (all $P > 0.05$).

In a confirmatory discriminant analysis with the nine pre-specified predictor variables entered in step-wise fashion (Table 3), and neuropathological diagnosis as the classification variable, a single discriminant function was identified ($\chi^2 = 17.289, df = 2, P < 0.001$). Examination of the structure matrix showed that two variables loaded strongly on this function and contributed maximally to group separation: the orientation-memory subtest of the ACE (F to remove = 9.643, Wilks $\lambda = 0.286, P < 0.001$) and the presence of frontal-lobe type behavioral change (F to remove = 9.643, Wilks $\lambda = 0.286, P < 0.001$).

Case 9: CBS with Alzheimer's Pathology

This 70-year-old right handed woman presented with a 3-year history of intermittent right upper limb myo-

TABLE 2. Cumulative clinical features of the 12 cases of corticobasal syndrome

Feature	Clinico-pathologic case series											
	1	2	3	4	5	6	7	8	9	10	11	12
Neuropathologic diagnosis	CBD	CBD	CBD	CBD	CBD	CBD	AD	AD	AD	AD	AD	AD
Age of onset (yr)	61	64	60	70	67	73	74	75	67	69	71	61
Duration of illness (yr)	5	5	9	4	5	11	5	13	11	13	13	3
Gender	M	M	M	M	F	F	M	F	F	F	F	M
Handedness	R	R	R	L	R	R	R	R	R	R	R	L
Most affected side	R	L/R ^a	R	L	L	L	L	R	R	L	L	L
Symptom onset to diagnosis (yr)	1	2	5	2	2	3	5	5	3	4	2	2
Survival time from disease onset (yr)	5	5	9	4	5	11	5	13	11	13	13	3
Survival time from diagnosis (yr)	4	3	4	2	3	8	1	8	8	9	11	1
Insidious onset; gradual progression ^b	P	P	P	P	P	P	P	P	P	P	P	P
Motor features												
Asymmetrical presentation ^b	P	P	P	P	P	P	P	P	P	P	P	P
Limb apraxia ^b	[Early]	[Early]	Early	Early	Early	[Early]	[Early]	[Early]	[Early]	[Early]	[Early]	[Early]
Orobuccal apraxia	–	Mid	[Early]	–	Mid	[Early]	–	–	–	–	–	–
Extrapyramidal signs ^b	–	Mid	Mid	Mid	Mid	Early	[Early]	Late	Mid	Late	–	Late
Myoclonus ^b	–	–	Mid	–	–	Early	Late	–	–	–	–	Late
Dystonia ^b	Mid	–	–	–	–	Early	–	–	–	–	–	–
Oculomotor apraxia	–	Mid	Mid	Mid	Mid	Mid	–	Late	–	Late	–	–
Dysarthria	–	–	Mid	–	Mid	–	–	[Early]	–	–	–	–
Dysphagia	Late	Late	–	–	Late	–	–	–	–	–	–	–
Gait/postural instability	–	Mid	–	Late	Late	–	Late	–	–	–	–	–
Cerebral cortical features												
Alien hand phenomenon ^b	[Early]	Mid	Mid	Mid	–	[Early]	Late	–	[Early]	–	Mid	Mid
Cortical sensory loss ^b	–	–	Mid	Mid	–	–	Late	–	Mid	–	–	Mid
Visuospatial syndrome	–	–	–	[Early]	–	–	–	–	–	[Early]	[Early]	–
Frontal release signs	Early	Mid	Mid	Mid	Early	Mid	Late	Late	Mid	–	–	Mid
Utilization behaviour	[Early]	–	–	[Early]	[Early]	–	–	–	–	–	–	–
Gegenhalten phenomenon	Mid	Mid	–	–	Mid	–	–	–	–	–	–	–
Cognitive and behavioural features												
Initial episodic memory	–	–	–	–	–	–	Early	[Early]	[Early]	–	Early	[Early]
Language impairment (NFA) ^b	Early	[Early]	[Early]	–	[Early]	–	–	–	–	–	Late	–
Personality and behaviour	Mid	Mid	Mid	[Early]	Early	Mid	–	–	–	–	–	Mid
Visual spatial deficits ^b	–	–	P	P	P	P	P	P	P	P	P	P
Signs of frontal-executive dysfunction ^b	P	P	P	P	P	P	P	P	P	–	P	P
Change in food preference	–	Mid	Mid	Early	Mid	–	–	Late	–	–	–	–
Initial ACE total score	–	76	66	87	68	70	44	–	50	50	41	49
Initial MMSE	20	24	22	27	22	21	16	22	15	23	12	18
Neuroimaging features												
MRI atrophy pattern	NA	FP	NA	PO	FP	N	NA	NA	TP	NA	T/HC	TP
SPECT	NA	L>R gen	L FP	Bil FT	FP	Bil FP, L T	NA	NA	L TP	Bil TP	NA	NA

Early, initial dominant feature; [Early], presenting symptom; Mid, features seen in the middle 1/3rd of the illness; Late, features appearing during the last 1/3rd of the illness; – = features not present or not stated in case record; P, present; FP, frontoparietal; TP, temporo-parietal; Bil, bilateral; L, left; R, right; NA, no available data; ACE, Addenbrooke cognitive examination; MMSE, mini mental state examination.

^aDissociated laterality: dyspraxia on the left; extrapyramidal signs on the right.

^bDiagnostic features of proposed criteria [Ref. 20].

clonic jerks. In addition, and noted that her right upper limb “won’t do what I want it to do”, she had difficulty in writing, dressing, fastening buttons, and using cutlery. Approximately 18 months after the onset of these motor problems, she developed impairment of episodic memory and difficulty with calculations and word finding. Family and past medical history were unremarkable.

Neurological examination revealed severe right upper limb ideomotor dyspraxia worse for meaningless gestures but also affecting miming of transitive ges-

tures, and mild extrapyramidal rigidity, bilateral asymmetric (right > left) spontaneous myoclonic finger jerks, right left disorientation, bilateral agraphesthesia, and severe dysgraphia. Her right hand adopted awkward positions while walking. Bedside cognitive examination showed abnormalities in attention, orientation, anterograde memory and particularly visuo-constructive tasks.

Neuropsychological evaluation confirmed severe memory impairment, reduced verbal fluency, dyscalculia, visuo-constructive impairment, and poor executive

TABLE 3. Analysis of predictor variables

Predictor variable	LR	P
Initial episodic memory	10.9	0.001
Initial visuospatial presentation	0.5	0.50
Initial nonfluent language impairment	7.6	0.006
Eating behavior	3.3	0.07
Frontal-lobe type behavior	10.9	0.001
Utilization behavior	7.6	0.006
Oculomotor apraxia	3.3	0.07
Oculobucco-facial apraxia	7.6	0.006
ACE OM subtest score	10.9	0.001

LR, likelihood ratio.

functions. There was a moderate degree of cortical atrophy on MRI, most marked posteriorly, and particularly on the left, with SPECT showing left fronto-temporal parietal perfusion deficits.

Over the next 3 years, the dyspraxic extrapyramidal and memory components worsened. Two years post presentation, she scored 15 and 50 on the MMSE and ACE. Neurological examination showed delayed saccadic initiation with normal range of eye movements, severe bilateral upper limb apraxia, rigidity, and cogwheeling (right more than the left), positive frontal release reflexes (pout, palmomental and glabellar), but preserved gait and balance. After 6 years, she was bed-bound and mute.

Neuropathology

The whole brain weighed 920 g. The left hemisphere showed severe cerebral gyral atrophy and sulcal widening, with an emphasis on frontal and anterior parietal lobes. Coronal slices of the left hemisphere confirmed the moderately severe degree cortical and the medial temporal lobe atrophy. Transverse section through the hemi-brainstem showed mild pallor of the substantia nigra and moderate pallor of the locus coeruleus. Microscopic examination showed very extensive (Braak stage V) Alzheimer-type pathology in all cortical regions.

In summary, although she had the typical hallmarks of CBS as evidenced by a constellation of extreme dyspraxia in conjunction with pronounced extrapyramidal signs, the impressive early deficit in episodic memory and absence of language or behavioral changes were indicators of the underlying AD pathology.

DISCUSSION

All 12 patients were assessed by a behavioral neurologist with extensive experience of neurodegenera-

tive disorders and diagnosed in life as having classic CBS which is not traditionally regarded as a presenting feature of Alzheimer's disease. Moreover, all 12 fulfilled strict diagnostic criteria yet half had Alzheimer's disease and not CBD. Despite significant progress, current clinical classifications do not accurately predict the underlying specific pathological process. Our study takes this area forward by identifying a set of clinical and cognitive variables which may help to determine the pathological substrate of CBS in vivo. Furthermore, we have also added to growing awareness of the overlap between clinical features of CBD and AD, in terms of its atypical phenotypic look-alike features reminiscent of CBD.

Two independent predictors were found to distinguish accurately between AD and CBD: initial episodic memory complaints for the AD group, and frontal-lobe type behavioral symptomatology in the CBD group. No CBD patient had early episodic memory complaints whereas none of the patients with AD had frontal-lobe type behavioral changes. Moreover, three other clinical variables: (1) initial nonfluent language impairment, (2) orobuccal apraxia, and (3) presence of utilization behavior showed significant associations with CBD pathology during life. In contrast, alterations in eating behavior, initial visuospatial features and oculomotor apraxia were not reliable distinguishing features.

The combined orientation-memory subtest score of the ACE¹⁹ was found to be abnormal in all patients in the CBS-AD group in keeping with their early episodic memory complaints. The relatively preserved episodic memory functioning in CBD is in accordance with a recent finding that such patients perform better on the memory subtest of the Dementia Rating Scale (DRS) than those with AD.²⁷ Memory impairment in classic CBD has been ascribed to the poor use of strategic processes in encoding and retrieval, arising from executive dysfunction or disruption of frontal-subcortical circuits.²⁷ Supportive evidence for this assertion comes from a recent autopsy study correlating the relative preservation of episodic memory in pathologically confirmed CBD with mild or absent neuronal loss and less tau-immunoreactivity in the hippocampus and temporal lobe.¹⁸ We assume that the early episodic memory impairment reflects involvement of the medial temporal lobe in the CBS-AD group.

In our cohort of patients with CBD, the frontal-lobe type behavioral disturbance typically included a combination of apathy, irritability, socially inappropriate disinhibited behavior, emotional lability, stereotypic behavior, and the lack of insight. Other neuropsychiatric disturbances included depression, agitation, aggres-

sion, anxiety, intractable shouting, and outbursts of rage. Such neuropsychiatric and behavioral alterations, and particularly apathy, mood disturbance, disinhibition and obsessive-compulsive symptoms have reported.^{28–30} Recently, behavioral disturbance was described in 22% of 36 pathologically confirmed cases of CBD.³¹ Our work suggests that the presence of such behavioral features is one of the most important discriminators of CBD pathology from AD pathology during life, and confirms the importance of carefully documenting behavioral features in the clinical assessment of such patients.

Most of the classic CBD cases had forced grasping and/or utilization behavior which tended to occur early in the clinical course. No patient with AD pathology manifested frontal motor phenomena. Furthermore, several investigators have documented frontal involvement by neuropsychological evidence of dysexecutive abnormalities in CBD.^{32,33} Even brief bedside assessment, using verbal letter and category fluency, has been reported to be useful and sensitive in detecting the signs of frontal dysexecutive dysfunction in patients with CBD.^{27,34}

Initial features of nonfluent aphasia with disrupted articulation, and/or phonological speech errors were also predictors of CBD pathology, and supports the growing evidence for an overlap between CBD and primary progressive aphasia.^{21,35} A comprehensive review highlighted that of 42 studies (399 patients), 34% of clinically diagnosed CBD and 44% with pathologically confirmed CBD had associated aphasia.³⁶ Recent work investigating the neural associations of speech production disorder in progressive nonfluent aphasia highlighted the role of the left anterior insular cortex, frontal operculum, and inferior frontal gyrus (BA 44/47).³⁷ Language dysfunction was also documented to be an early feature in the autopsy-confirmed CBD series which correlated with tau pathology in the frontal gray matter and white matter.¹⁸ Non-fluency is reported to be the result of a combination of varying degrees of speech apraxia and syntactic processing deficits; it is of interest therefore that the majority of patients with a nonfluent presentation also had early, prominent oro-bucco-facial apraxia. Apraxia of speech (AOS) is typically misclassified as dysarthria but is important to recognize as it has implications for management and prediction of pathology because it has been strongly associated with underlying tau pathology.³⁸ It would be of interest for future investigations to assess the relative contributions of motor articulatory deficits and higher-order language processing such as syntactic processing in CBD.

The presence of orobuccal apraxia also distinguished the two groups (CBD > AD), and may also be useful in differentiating CBD from idiopathic Parkinson's disease and other atypical parkinsonian syndromes where it is typically absent. The presence of orobuccal apraxia is related to the simultaneous pathological involvement of parietal lobule and supplementary motor area.³⁹ The fact that both nonfluent aphasia and apraxia of speech and orobuccal apraxia are more common in CBD than CBS-AD reflects the more asymmetric distribution of pathology in the CBD group.

Asymmetrical extrapyramidal symptoms are recognized as one of the hallmarks of CBD²⁰ but were also present in all six patients with CBS-AD. Extra pyramidal signs such as akinesia and rigidity are known to occur in late stages of AD,⁴⁰ but are not generally accepted as a presenting feature of AD. Another typical motor feature of CBD, the flexed, dystonic unilateral upper limb posture, was observed only in two of our cases. Although previous autopsy-confirmed CBD series have emphasized an asymmetry of extrapyramidal features, rigidity, bradykinesia, apraxia, and a "useless arm" as hallmarks of CBD, our study did not document these clinical features as distinguishing CBD from AD.^{5,28,41,42}

One rather surprising finding was the absence of alternative pathologies that have been reported in association with CBS, notably PSP and FTLD with ubiquitin/TDP-43 positive inclusions and FTLD with tau-positive Pick bodies.^{3,5,13,16,17} The prevalence of AD pathology in our cohort was also higher than in other clinico-pathological series^{5,10,18} although there is a growing number of case reports of CBS associated with AD pathology.^{5,12} These differences probably reflect variation in the patterns of ascertainment and referral. Our Disorders of Movement and Cognition Clinic was established to evaluate and manage patients with complex syndromes involving aspects of cognition and motor control: of 17 patients evaluated over a 7 year period, 12 were followed to death and are reported here. It is quite likely that other clinics evaluating fewer such patients would have a higher prevalence of non-AD pathology. Nevertheless, all of our patients fulfilled strict criteria for CBS and had prominent apraxia as an early or presenting feature as shown in Table 2.

In conclusion, current diagnostic criteria for CBS do not distinguish between cases with classic CBD pathology and clinically similar cases of AD. Our findings of prominent nonfluent language dysfunction, early behavioral abnormalities emphasize a predominantly frontal and parietal distribution of disease in addition to the basal ganglia in CBD, but with less involvement of the medial temporal lobe structures. We have identi-

fied a pattern of clinical predictor variables that appear to be good candidates to discriminate CBD from AD related CBS in vivo; this needs further validation in a larger prospectively assessed cohort.

Author Roles: B. Shelley, C. Kipps: data analysis, drafting of manuscript. T. Bak, J. R. Hodges: Clinical diagnosis and followup, neurological examination, neuropsychological and neuropsychiatric assessment, editing of manuscript. J. Xurueb: neuropathological diagnosis and description.

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