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Symmetric corticobasal degeneration (S-CBD)

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Abstract

Background—Corticobasal degeneration (CBD) is a neurodegenerative disease characterized pathologically by neuronal loss, gliosis and tau deposition in neocortex, basal ganglia and brainstem. Typical clinical presentation is known as corticobasal syndrome (CBS) and involves the core features of progressive *asymmetric* rigidity and apraxia, accompanied by other signs of cortical and extrapyramidal dysfunction. Asymmetry is also emphasized on neuroimaging.

Objective—To describe a series of cases of CBD with symmetric clinical features and to compare clinical and imaging features of these symmetric CBD cases (S-CBD) to typical cases of CBS with CBD pathology.

Methods—All cases of pathologically confirmed CBD from the Mayo Clinic Rochester database were identified. Clinical records were reviewed and quantitative volumetric analysis of symmetric atrophy on head MRI using atlas based parcellation was performed. Subjects were classified as S-CBD if no differences had been observed between right- and left-sided cortical or extrapyramidal signs or symptoms. S-CBD cases were compared to 10 randomly selected typical CBS cases.

Results—Five cases (2 female) met criteria for S-CBD. None had limb dystonia, myoclonus, apraxia or alien limb phenomena. S-CBD cases had significantly less asymmetric atrophy when compared with CBS cases ($p=0.009$); they were also younger at onset (median 61 versus 66 years, $p<0.05$) and death (67 versus 73 years, $p<0.05$). Family history was present in 40% of S-CBD cases.

Conclusions—CBD can have a symmetric presentation, clinically and radiologically, in which typical features of CBS, such as limb apraxia, myoclonus, dystonia and alien limb phenomenon, may be absent.

Keywords

Corticobasal degeneration; Corticobasal syndrome; Symmetric CBD; Atlas Based Parcellation; Pathology

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Introduction

Corticobasal degeneration is a neurodegenerative disease of late middle age, characterized pathologically by neuronal loss, gliosis and tau deposition in gray and white neocortex, basal ganglia and brainstem [1]. It was first described in three cases by Rebeiz et al in 1968 as 'corticodentatonigral degeneration with neuronal achromasia [2]. The typical associated clinical presentation is known as corticobasal syndrome (CBS). The core clinical features of this syndrome are progressive *asymmetric* rigidity and apraxia accompanied by signs of cortical and extrapyramidal dysfunction. Typical cortical signs are alien limb phenomena, cortical sensory loss, myoclonus; extrapyramidal signs include dystonia, bradykinesia and tremor [3]. Impaired cortical and basal ganglia function can be supported by neuropsychological testing with attention, concentration, executive function, praxis, language and visuospatial domains affected [4,5]. Neuroimaging, structural and functional, supports the clinical diagnosis. Computed tomography and magnetic resonance imaging of the brain have demonstrated asymmetric cortical atrophy, especially frontoparietal, as well as basal ganglia, lateral ventricles and cerebral peduncles. Similarly, asymmetric hypoperfusion in single photon emission CT (SPECT) and hypometabolism on positron emission tomography (PET) of the parieto-frontal and/or basal ganglia have been reported [6–10]. Thus, the criteria for suspecting a clinical diagnosis of CBD focuses on asymmetry of key findings, clinically or radiologically.

Corticobasal syndrome accounts for approximately 50% of CBD case presentations [11]. There is significant clinical and pathological overlap in both CBS and CBD with other tauopathies, such as frontotemporal dementia with Parkinsonism linked to Chromosome 17 (FTDP-17), Pick's disease with Pick bodies and progressive supranuclear palsy (PSP) [11,20]. CBS is the most common clinical presentation of CBD. Others reported in the literature include progressive non-fluent aphasia [12,13], apraxia of speech [14], behavioral variant frontotemporal dementia, PSP [11] and dementia not otherwise specified [15]. Grimes et al [15] reported 13 postmortem cases of CBD and noted four cases had an antemortem diagnosis of CBS, while most presented with dementia. Murray et al [16] reported 15 cases of autopsy-confirmed CBD, of which the antemortem diagnoses were CBS (six cases), FTD (six cases) and PSP (two cases). Cognitive difficulties were noted to be as prominent as motor deficits on presentation. Variable clinical presentations and symptom progression of CBD likely reflect the cerebral location of pathological lesions rather than the actual histopathology itself. However, there is no literature reporting specifically symmetric onset and progression of clinical features.

Meanwhile, CBS can have different underlying pathological substrates [17]. Boeve and colleagues in 1999 published autopsy findings in 13 cases of CBS. The pathological diagnosis was CBD in seven, Alzheimer's disease (AD) in two; and one for each of Pick's disease; PSP, non-specific degenerative changes and Creutzfeld-Jakob disease. Shelley et al [18] reported 12 cases of CBS in life and of these fifty percent had CBD pathology and fifty percent had Alzheimer's pathology. Also reported are motor neuron inclusion body dementia [19] and dementia with Lewy bodies [20]. Interestingly, the sensitivity of diagnosing CBD correctly, even when the classic CBS clinical features are present, is low. Litvan et al showed a sensitivity of 33% in a simulated diagnostic study [21].

A neuropathological diagnostic criterion for CBD was updated in 2002 by a working group formed by Dickson and colleagues [1]. This emphasized a specific clinical phenotype is *not* required because of the known diverse clinical presentations. The pathological criteria require cortical and striatal tau-positive neuronal and glial lesions, astrocytic plaques and thread-like lesions in white and grey matter with neuronal loss in focal cortical regions and substantia nigra. Cortical atrophy, ballooned neurons and degeneration of substantia nigra are typically also present. Asymmetric atrophy is recognized but not essential for diagnosis. The clinical

symptoms and signs are believed to reflect the distribution and pattern of brain pathology which may have variable sites. Relatively less basal ganglia involvement but higher frontoparietal deposition will therefore have minimal extrapyramidal features while behavioral and frontal domains are preferentially affected. This is illustrated by Hu et al who compared patients with autopsy-proven AD and CBD pathology presenting as CBS clinically. AD patients with clinical CBS had similar characteristics to CBD patients, including core features and disease duration. Functional brain imaging could differentiate the two however, with parietal hypoperfusion in AD cases, and frontotemporal hypoperfusion in CBD cases [22].

Ultimately, *asymmetric* clinical signs and symptoms are emphasized in pathologically confirmed CBD. *Symmetric* clinical presentations including presence of symmetrical imaging findings, has not been emphasized or well described in the literature. We report five cases of historically symmetric cases of autopsy-confirmed CBD and contrast these with ten randomly selected cases of typical clinically asymmetric CBD.

Methods

Case Ascertainment

We identified all cases of pathologically confirmed CBD from the Mayo Clinic Rochester database between January 1993 and December 2007. All cases had been evaluated at least twice in the movement disorder and behavioral neurology subspecialty clinics. At death, all cases proceeded to post-mortem evaluation of a single hemisphere per autopsy protocol, at Mayo Clinic, and met established neuropathologic diagnostic criteria for CBD [1].

Clinical Assessment

The clinical records of all cases were retrospectively reviewed by two authors (AH, KAJ). All cases were examined at least twice (range two to ten visits, median four visits) between January 1991 and December 2007. Demographic and clinic features from time of initial presentation to final evaluation before death were abstracted. Gender, age at clinical onset, age at death, disease duration, clinical signs and symptoms, neuroimaging findings, and family history of neurodegenerative disease were reviewed. Disease duration was defined as the difference between age at onset and age at death. One or more first-degree relatives with a history of dementia and/or parkinsonism and/or motor neuron disease was considered positive for a family history of neurodegenerative disease.

Inclusion criterion for symmetric CBD (Box 1) was as follows: autopsy diagnosis of CBD based on current neuropathological criteria; no difference observed at any time in the disease course between right- and left-sided cortical or extrapyramidal signs or symptoms by the evaluating physician. Five cases met these criteria. These were compared to ten randomly selected typical CBS cases.

Radiographic Assessment

Volumetric head MRI scans were available in all five cases of symmetric CBD (age = 60 ± 11 , 40% female) and in five of the ten randomly selected typical CBS cases (age = 70 ± 4 , 100% female). An atlas-based parcellation technique was employed using SPM5 and the automated anatomic labeling (AAL) atlas in order to generate left and right grey matter volumes for the following regions of the brain for each subject: entire supratentorial hemisphere, central regions (including precentral gyrus, postcentral gyrus and paracentral lobule), frontal lobe, temporal lobe, parietal lobe, insula and striatum. An asymmetry score was calculated for each region for each subject using the following formula: $(\text{left volume} - \text{right volume}) * 2 / (\text{left volume} + \text{right volume})$. Asymmetry scores were also calculated for a control cohort of 30 healthy subjects (age = 61 ± 12 , 63% female).

Neuropathologic Assessment

Tissue obtained at the time of autopsy was examined as per neuropathological protocol. In all cases, pathology diagnosis of CBD was made by one of two neuropathologists (JEP, DWD). All cases were also re-reviewed in 2009 to ensure that older cases met recent published criteria for CBD, (1) by one neuropathologist (DWD). The neuropathological diagnosis of CBD was made using criteria that emphasized tau-immunoreactive lesions in cortical and subcortical regions in a characteristic distribution. This includes tau-positive neuronal and glial lesions, astrocytic plaques and extensive tau-immunoreactive lesions in cortical, subcortical and white matter regions [1]. (Fig. 1)

Statistical Analysis

Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc, Cary, NC) with α set at 0.05. All binary data were compared across symmetric CBD and CBS groups with Chi-square test (Fishers Exact test was used for cells with small numbers), while Mann-Whitney U test was used to compare continuous data across both groups.

Results

For the years 1993 to 2007, we found 31 cases that met the pathological diagnosis of CBD. Of these, five cases (16%) met criteria for symmetric CBD. (Table 1). Two of the five cases were female. The antemortem clinical diagnoses were behavioral variant frontotemporal dementia in three cases, and one case each of frontotemporal dementia with Parkinsonism and atypical AD. The presence of clinical symptoms and signs were contrasted between both groups, independent of whether the feature was symmetric or asymmetric. Grouping the signs into motor, behavioral, apraxia, cognitive, language and sleep highlighted the differences. Behavioral changes were prominent in symmetric CBD and absent in CBS. On the contrary, language abnormalities, limb apraxia and several motor features (axial rigidity, bradykinesia, myoclonus, alien limb, Babinski sign) were prominent in CBS and absent in symmetric CBD cases. Both groups had motor findings of limb rigidity, falls, parkinsonism, rest tremor, gaze palsy, hyper-reflexia, dysphagia and cognitive changes of memory impairment and acalculia. (Table 2, Fig. 2). Motor features when present in symmetric CBD were symmetric affecting both sides equally.

Age of onset was 61 (median) (range 40–69) for symmetric and 66 (median) (61–73 range) for asymmetric cases. Age at death was 67 (range 47–69) and 72.5 (range 67–80) respectively. Compared to typical cases of CBS, those with symmetric CBD were younger at onset (median 61 versus 66 years, $p<0.05$) and younger at death (67 versus 73 years, $p<0.05$). However, both groups had similar disease duration (5 versus 6 years, $p=0.20$). There was no gender preference; 40% of symmetric and 50% of typical CBD cases were female. (Table 3).

Family history of neurodegenerative disease was different between both groups; 40% in symmetric cases and 10% in asymmetric cases although this did not reach significance. ($p=0.24$). In the symmetric CBD group, one case had a maternal grandfather with Pick's disease (genetic testing was not performed in this case). A second case had a paternal uncle with a parietal lobe syndrome, and interestingly another paternal uncle with Creutzfeldt Jakob disease. *MAPT* genetic testing in this patient was negative.

All symmetric CBD cases had symmetric atrophy on visual inspection of their head MRI brain scans. (Table 4). A typical imaging example is demonstrated in Fig 3. Using atlas based parcellation, the asymmetric CBD group had a significantly greater hemispheric asymmetry score than the symmetric CBD group ($p=0.009$) (Table 5). The asymmetric CBD group showed

significantly greater asymmetry in regions of the brain surrounding the central sulcus ($p=0.004$) and the striatum ($p=0.03$), with a trend for greater asymmetry in the temporal lobe ($p=0.06$), compared to the symmetric CBD group. Asymmetry scores in the symmetric CBD group were not significantly different from controls. There was a slight trend for increased asymmetry in the frontal lobe ($p=0.09$), primarily in the medial frontal lobe compared to controls.

Pathological re-examination of all 15 CBD cases showed features typical of CBD with one S-CBD case (case 2; negative *MAPT* gene testing) showing severe thalamic pathology.

Conclusions

Corticobasal degeneration is traditionally suspected on the basis of asymmetric signs and symptoms in life. However the five cases we describe illustrate the fact that CBD can present as a symmetric syndrome. In these cases core features of CBS such as limb apraxia, myoclonus, dystonia and alien limb phenomenon may not be present. In addition, MRI neuroimaging demonstrated symmetric hemispheric atrophy in all five cases which was significantly different from typical CBS cases with quantitative analysis.

Symmetric presentations of CBD have earlier disease onset in this sample group, and earlier age of death, with similar disease duration to typical asymmetric subjects. Interestingly, a positive family history of neurodegenerative disease was higher in the S-CBD cases. CBD is traditionally considered a sporadic disorder, thus there may be a genetic predilection to development of symmetric degeneration. The reason for the differences between the two groups is unclear but suggests that symmetric CBD may be different from the more typical asymmetric variant presenting as CBS. Similar to PSP where it has been suggested that asymmetric PSP presenting as Parkinson's disease should be designated PSP-P [23] we suggest that symmetric CBD be designated S-CBD to differentiate and separate the symmetric variants. This designation would allow future studies to determine whether S-CBD is a genetically or pathologically unique clinico-pathologic-genetic entity. One patient did have testing for mutation in the tau gene and was negative suggesting that S-CBD is simply not FTL-17.

The quantitative MRI analysis was validation that the S-CBD group had significantly less asymmetry than the CBS group in regions of the brain that are typically associated with typical CBD [24], namely regions surrounding the central sulcus (precentral gyrus, postcentral gyrus and paracentral lobule) and the striatum. No significant difference was observed between the S-CBD group and controls although there was a slight trend for differences in the frontal lobe in the S-CBD subjects compared to controls which can be explained by the fact that the majority of S-CBD subjects had a clinical diagnosis of behavioral variant FTD which would be expected to target the frontal lobes.

Unfortunately, we are unable to determine whether S-CBD is also symmetric pathologically due to the universal protocol of examining one hemisphere only at autopsy. Typical CBD pathology is reported to be asymmetric but the exact prevalence is unknown. However, if MRI volumetric analysis is used as a surrogate for macroscopic pathological atrophy, it would appear that this too is symmetric, although we cannot comment on microscopic lesion deposition.

Limitations of our study are that it is a retrospective analysis of small numbers of patients evaluated over many years. There may be a referral bias to our institution for diagnostically complex cases of neurodegenerative disease. Thus symmetric case may be rarer than they appear in this review. Conversely, there may in fact be a more common symmetric presentation of CBD but the diagnosis is not considered due to the emphasis on asymmetrical findings in CBD.

The strengths of the study are that all cases were clinically evaluated at one institution, all cases were evaluated by specialists in movement disorders and behavioral neurology, all cases had multiple clinical evaluations, all cases were re-reviewed by an expert neuropathologist, and the application of an unbiased quantitative method, atlas based parcellation, to validate our clinical MRI findings.

It is therefore important to again highlight that not all cases of CBD will meet clinical criteria for CBS. Although the diagnosis is typically made when the clinical presentation is relatively classic, there is still low sensitivity. The best predictors are limb dystonia, alien limb, asymmetric Parkinsonism, ideomotor apraxia and absence of gait or balance disorder in one study reported by Litvan et al, and supported by asymmetry on neuroimaging [21]. However at best this still misses a significant proportion of antemortem CBD diagnoses. Emphasizing the presence of asymmetric features may sway the clinician from considering CBD as a diagnosis. Predicting underlying CBD pathology in cases not presenting as CBS can be difficult, but we suggest it is more likely to occur in patients presenting less than age 65 years old, and may be more likely in those with a positive family history of neurodegenerative disease. At present, the gold standard for CBD diagnosis remains neuropathological. Hence the continuing importance of post-mortem analysis of neurodegenerative diseases to further refines the phenotype and frequency of antemortem clinical presentations. Separating S-CBD could lead to important genetic discoveries.

Box 1: Clinicopathologic criteria for S-CBD

- Pathological diagnosis of CBD based on current neuropathological criteria
- Absence of asymmetric signs and symptoms at presentation and during the disease course
- Relative absence of asymmetric frontoparietal atrophy on head MRI
- Relative absence of asymmetric frontoparietal hypometabolism or hypoperfusion on PET and SPECT

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Ballooned neurons in superior frontal cortex.
(Left: HE x 400; right alpha-beta-crystallin x 400)

Astrocytic plaques and pre-tangle in
superior frontal cortex.
(Tau x 400)

Nigral pigmented neuron containing a
“corticobasal body”. An unaffected
neuron is also seen
(HE x 400)

Oligodendroglial “coiled
body” in superior frontal
white matter
(Tau x 400)

“Corticobasal body”
(Tau x 400)

Figure 1.
Symmetric-CBD neuropathology

(a)

(b)

Figure 2.

(a) Frequency of motor signs/symptoms and apraxia in CBS versus S-CBD. (b) Frequency of behavioral, cognitive and language symptoms / signs in CBS versus S-CBD.

Figure 3.
Symmetric atrophy in a symmetric-CBD case.
T1 MRI brain coronal slices demonstrating symmetric cerebral atrophy in a symmetric-CBD case.

Table 1
Comparison of clinical features of symmetric and typical (asymmetric) CBS cases.

Case	Gender	Clinical diagnosis	Onset (yrs)	Death (yrs)	Duration (yrs)	Family history ¹
1	F	Atypical AD	69	73	4	Negative
2	M	bvFTD	52	57	5	Positive
3	M	bvFTD	61	67	6	Negative
4	F	bvFTD	40	47	7	Negative
5	M	FTDP	63	67	4	Positive
6	F	CBS	65	73	8	Negative
7	F	CBS	69	75	6	Negative
8	F	CBS	73	80	7	Negative
9	M	CBS	72	77	5	Negative
10	M	CBS	66	70	4	Negative
11	M	CBS	63	67	4	Negative
12	M	CBS	65	72	7	Positive
13	F	CBS	61	67	6	Negative
14	M	CBS	70	76	6	Negative
15	F	CBS	63	69	6	Negative

AD Alzheimer's disease
bvFTD Behavioral variant frontotemporal dementia
FTDP Frontotemporal dementia with parkinsonism
CBS Corticobasal degeneration
¹ Positive family history defined as one or more first-degree relatives with a history of dementia and/or parkinsonism and/ or motor neuro disease

Table 2

Comparison of frequency of symptoms and signs in CBS versus S-CBD cases

Symptoms /signs	S-CBD cases (n=5)	Asymmetric CBS cases (n=10)
Motor		
Axial rigidity	0	1
Limb rigidity	1	5
Falls	1	3
Rest tremor	2	5
Bradykinesia	0	6
Gaze palsy / diplopia	3	1
Dystonia	0	3
Myoclonus	0	2
Alien limb	0	1
Babinski sign	0	2
Parkinsonism	3	4
Hyper-reflexia	2	4
Dysarthria	0	1
Dysphagia	1	1
Apraxia		
Limb ideomotor apraxia	0	7
Dressing apraxia	0	1
Cognitive		
Visuospatial difficulty	1	0
L/R discrimination difficulty	0	1
Acalculia	2	1
Memory impairment	1	1
Language		
Effortful speech	0	5
Word-finding difficulty	0	2
Echolalia	2	0
Behavior		
Frontal lobe signs	2	0
Behavior/personality change	3	0
Withdrawn	1	0
Apathy	2	0
Executive dysfunction	1	0
Disinhibition	2	0

Symptoms /signs	S-CBD cases (n=5)	Asymmetric CBS cases (n=10)
Sleep		
Dream enactment behavior	2	0

Table 3

Comparison of demographics in symmetric CBD (S-CBD) and typical asymmetric CBD (CBS) cases.

	Symmetric CBD (n=5)	Asymmetric CBD (CBS) (n=10)	P value
Age of onset (median)	61 (range 40–69)	66 (range 61–73)	(p<0.05)
Age at death (median)	67 (range 47–69)	73 (range 67–80)	(p<0.05)
Disease duration (yrs)	5	6	(p=0.20)
Gender	2 (40%) female	5 (50%) female	
Family history of neurodegenerative disease	2 (40%)	1 (10%)	(p=0.24)

Table 4

Comparison of radiological features of symmetric S-CBD and typical (asymmetric) CBS cases

Case	MRI FINDINGS	PET/SPECT FINDINGS
1	Mild generalized atrophy	NP
2	Mild bifrontal atrophy	NP
3	Mild generalized atrophy	Hypometabolism right frontal (PET)
4	Bifrontotemporal atrophy	Bifrontal reduced perfusion (SPECT)
5	Bifrontal atrophy	Bifrontal reduced perfusion (SPECT)
6	Minimal atrophy	Left temporoparietal reduced perfusion (SPECT)
7	Normal	Right temporoparietal reduced perfusion (SPECT)
8	Bitemporal atrophy, R>L (PET)	Hypometabolism left frontoparietal, BG, cerebellum
9	N/A	Left temporal, frontoparietal reduced perf (SPECT)
10	N/A	Right >left parietotemporal reduced perf (SPECT)
11	Generalized atrophy (N/A)	NP
12	Generalized atrophy (N/A)	N/A
13	Asymmetric atrophy	NP
14	Mild generalized atrophy	NP
15	Mild generalized atrophy	N/A

PET Positron emission tomography

SPECT Single photon emission CT

N/A Not available

NP Not performed

L/R Left/Right

Table 5

Absolute asymmetry scores for the symmetric and asymmetric CBD groups and controls

Region	Controls	Symmetric CBD (S-CBD)	Asymmetric CBD (CBS)	P value: Symmetric CBD vs. controls	P value: Asymmetric CBD vs. controls	P value: Asymmetric CBD vs. symmetric CBD
Supratentorial hemisphere	0.01 (0.01)	0.03 (0.03)	0.10 (0.03)	0.12	0.004	0.009
Central regions	0.04 (0.04)	0.03 (0.02)	0.17 (0.06)	0.33	0.01	0.004
Striatum	0.04 (0.03)	0.03 (0.03)	0.16 (0.09)	0.40	0.046	0.03
Insula	0.05 (0.03)	0.07 (0.03)	0.16 (0.14)	0.29	0.16	0.23
Frontal lobe	0.03 (0.01)	0.09 (0.06)	0.09 (0.05)	0.09	0.056	0.88
Temporal lobe	0.06 (0.03)	0.06 (0.01)	0.13 (0.06)	0.98	0.056	0.06
Parietal lobe	0.09 (0.04)	0.08 (0.05)	0.07 (0.04)	0.71	0.34	0.69