Diffuse Lewy Body Disease Presenting As Corticobasal Syndrome

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INTRODUCTION

- **Corticobasal syndrome (CBS)** is characterized by a constellation of signs and symptoms including limb apraxia, cortical sensory loss, myoclonus and alien limb sign, as well as bradykinesia, dystonia, tremor and asymmetric rigidity.
- Several neuropathological processes can produce CBS, including Alzheimer's disease (AD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). Few reports have described autopsy-confirmed diffuse Lewy body disease (DLBD) presenting as CBS.
- **It remains unclear if DLBD can present with a focal cortical syndrome such as CBS.**
- **We addressed this gap in knowledge by reviewing DLBD cases from a brain bank of neurodegenerative disorders at Mayo Clinic.**

OBJECTIVES

AIM: To describe clinical and pathologic characteristics of diffuse Lewy body disease (DLBD) presenting as corticobasal syndrome (CBS).

MATERIAL & METHODS

MATERIALS

- **STUDY SAMPLES:** 523 autopsy-confirmed cases of DLBD from Mayo Clinic brain bank for neurodegenerative disorders.
- We **identified 11 patients diagnosed with CBS.**
- For comparison, we studied **22 DLBD brains with antemortem presentation of dementia with Lewy bodies (DLB)**.

METHODS

- **CLINICAL ASSESSMENT:** Information was obtained through a review of medical records (see **Table 1**).
  Using features from diagnostic criteria, the focus was on the following: **1) CBS clinical features,** noting any asymmetry, including limb rigidity, limb dystonia, limb myoclonus, limb apraxia, cortical sensory loss, and alien limb phenomena; **2) DLB clinical features** including progressive cognitive decline, fluctuation, visual hallucinations, dream enactment behavior, and features of parkinsonism, **3) other neurologic signs** such as cervical dystonia, pyramidal signs, vertical gaze palsy, axial rigidity, dysphagia, expressive aphasia.
- **PATHOLOGIC ASSESSMENT:** In addition to histologic evaluation, presence and severity of **Alzheimer pathology** was assessed with **thioflavin S fluorescent microscopy and a Braak neurofibrillary tangle stage and Thal amyloid phase** were assigned. **Lewy-related pathology** was assessed with **immunohistochemistry for α-synuclein** in five regions of neocortex, as well as amygdala, olfactory bulb (if available), basal forebrain and brainstem. The method used for α-synuclein immunohistochemistry (rabbit polyclonal (NACP), 1:3000 with 95% formic acid pretreatment and DAKO Envision Reagents) gives comparable sensitivity to other methods.
- Given previous studies suggesting importance of pathology in peri-Rolandic cortices in CBS, **we used digital pathology to count Lewy bodies and to quantify intracytoplasmic and neuritic α-synuclein and phospho-tau burden in the motor cortex.**

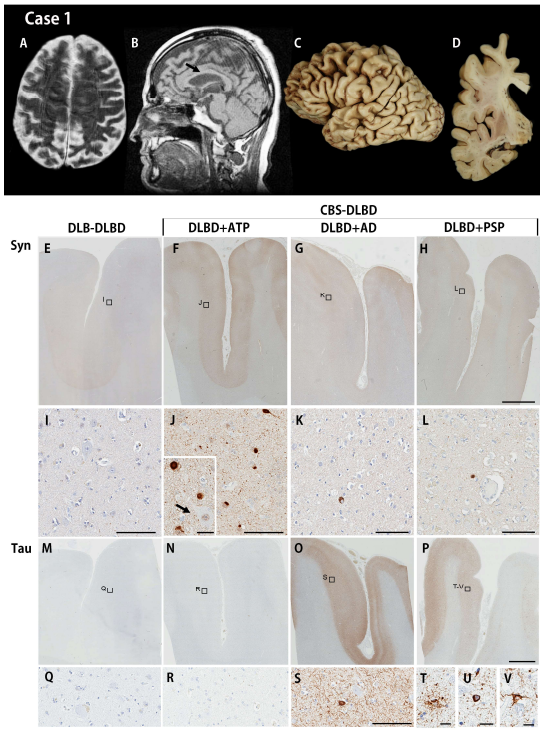
RESULTS

TABLE 1. Demographic and clinical features of DLBD presenting as CBS compared to DLBD presenting as DLB

Demographic and Clinical Features	CBS-DLBD (N=11)	DLB-DLBD (N=22)	P value
Males, N (%)	6 (55)	18 (82)	0.12
Age at onset, y, median (Q1, Q3)	58 (51, 64)	71 (65, 75)	0.005
Age at death, y, median (Q1, Q3)	65 (57, 71)	77 (72, 84)	0.003
Disease duration, y, median (Q1, Q3)	6 (5, 7)	8 (5, 8)	0.36
CBS clinical features (Armstrong 2013), N (%)			
Limb rigidity	11 (100)	16 (73)	0.077
Asymmetric	8 (73)	4 (18)	0.005
Limb dystonia	8 (73)	1 (5)	0.001
Asymmetric	7 (64)	0 (0)	< 0.001
Limb myoclonus	10 (91)	2 (9)	< 0.001
Asymmetric	7 (64)	2 (9)	0.002
Limb apraxia	11 (100)	0 (0)	< 0.001
Asymmetric	10 (91)	0 (0)	< 0.001
Cortical sensory deficit	2 (18)	0 (0)	0.1
Alien limb phenomena	3 (27)	0 (0)	0.03
DLB clinical features (McKeith 2017), N (%)			
Progressive cognitive decline	11 (100)	22 (100)	-
Core clinical features			
Fluctuating cognition and alertness	6 (55)	15 (68)	0.47
Recurrent visual hallucinations	5 (45)	16 (73)	0.15
Probable REM sleep behavior disorder	2 (18)	16 (73)	0.009
Cardinal features of parkinsonism*			
Bradykinesia	11 (100)	18 (82)	0.28
Rest tremor	10 (91)	7 (32)	0.11
Supportive clinical features			
Sensitivity to antipsychotic agents	noted in one case	noted in two cases	-
Postural instability	10 (91)	13 (59)	0.11
Repeated falls	8 (73)	7 (32)	0.06
Hypersomnia	6 (55)	15 (68)	0.47
Hyposmia	noted in one case	not assessed	-
Levodopa responsiveness, N/number of prescribed cases, %	4/6 (66)	8/11 (73)	1.0
Other neurologic features, N (%)			
Pyramidal signs	6 (55)	0 (0)	< 0.001
Vertical gaze palsy	3 (27)	0 (0)	0.03
Axial rigidity	8 (73)	1 (5)	< 0.001
Dysphagia	3 (27)	0 (0)	0.03
Expressive aphasia (not fluctuating)	3 (27)	0 (0)	0.03

RESULTS

FIGURE1. Neuroimaging and neuropathologic features of DLBD presenting as CBS.



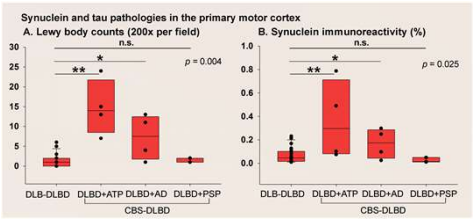
A-B. Antemortem MRI (T1) of DLBD presenting as CBS (Case 1 in Table 1)Note widening of frontoparietal sulci and thinning of the corpus callosum. **C-D.** Macroscopic images show disproportionate cortical atrophy in frontoparietal cortices, including peri-Rolandic and premotor cortices. **E-V.** Immunohistochemistry of motor cortex. α-Synuclein (E-L) and phospho-tau (M-V). In DLBD presenting as CBS, α-synuclein pathology is more severe (F, J) than in DLBD presenting as DLB (E, G-I, K-L). Lewy-related pathology (including cortical Lewy bodies and Lewy neurites) is marked in lower cortical layers (layers IV-V). (J). Lewy bodies adjacent to a Betz cell (arrow in J, inset). The numbers of Lewy bodies in CBS with DLBD+AD (K, arrow), as well as CBS with DLBD+PSP (L, arrow) are less than in CBS with DLBD+ATP (see F and J). Tau pathology is less in CBS with DLBD+ATP (N, R) than in CBS with DLBD+AD (O, S) and in CBS with DLBD+PSP (P, T-V). In CBS with DLBD+PSP note presence of typical tau lesions of PSP (tufted astrocyte (T), coiled body (U) and pretangle (V)). Bars: E-H, M-P = 3 mm; I-L, Q-S = 100 μm; J, inset, T-V = 25 μm.

TABLE 2. Neuropathological characteristics of DLBD presenting as CBS and of DLBD presenting as DLB

	CBS-DLBD (N = 11)	DLB-DLBD (N = 22)	P-value
Brain weight, mean (Std. Dev.)	1124 (126)	1221 (133)	0.052
Thickness of corpus callosum (mm), median (Q1, Q3)	3.7 (3.2, 4.7)	4.6 (4.2, 5.1)	0.026
DLB likelihood (CDLB) (Intermediate : High)	6:5	6:16	0.15
Braak NFT stage, median (Q1, Q3)	V (IV, V)	IV (IV, V)	0.26
Thal amyloid phase, median (Q1, Q3)	4 (4, 5)	5, (4, 5)	0.52
Motor cortex pathologies, median (Q1, Q3)			
1. Lewy body counts	7 (1, 13)	1 (0, 2)	< 0.001
2. Synuclein burden (%)	0.1 (0.03, 0.3)	0.05 (0.02, 0.1)	0.11
3. Tau burden (%)	0.83 (0.22, 3.5)	0.02 (0.009, 0.31)	0.003
4. Spongiosis score	0 (0, 1)	0 (0, 0)	0.002
5. Betz cell neuronal loss score	0 (0, 0)	0 (0, 0)	1.0
Lewy body counts in other cortices, median (Q1, Q3)			
Parahippocampal gyrus	25 (16, 27)	25 (15, 26)	0.79
Anterior cingulate gyrus	17 (12, 28)	16 (12, 17)	0.18
Superior frontal gyrus	22 (10, 31)	8 (6, 14)	0.007
Middle frontal gyrus	12 (7, 20)	6 (4. 11)	0.017
Superior temporal gyrus	18 (12, 25)	16 (9, 21)	0.18
Inferior parietal lobule	9 (5, 20)	5 (3, 8)	0.05
Neuronal loss scores in brainstem, median (Q1, Q3)			
Substantia nigra (midbrain)	2 (2, 3)	2 (2, 3)	0.64
Locus ceruleus (pons)	1 (1, 2)	3 (1, 3)	0.016
Dorsal motor nucleus of vagus (medulla)	3 (1, 3)	2 (1, 3)	0.39

- There were no significant difference regarding Thal amyloid phase or Braak tau staging between the two DLBD groups.

FIGURE 2. Quantification of Lewy bodies and α-synuclein in the primary motor cortex



A-B: Cases of CBS-DLBD+ATP and those with DLBD+AD have more Lewy bodies and greater α-synuclein burden than DLBD presenting as DLB

SUMMARY AND CONCLUSION

- In this study, we highlight the fact that, while rare, **DLBD can also be found in patients with CBS,** and in four cases with only mild-to-moderate concomitant Alzheimer or tau pathology, **atypical cortical Lewy-related pathology may be the best neuropathologic correlate for the syndrome, suggesting a frequency of approximately 0.8% (4/523).**
- To our knowledge, this is the first report providing neuropathologic evidence that atypical distribution of Lewy-related pathology, with severe pathology in primary motor cortex, can present with CBS.
- These four cases had DLBD with only mild to moderate Alzheimer type pathology and no other pathologic explanation for CBS. These cases had **14-fold more Lewy bodies and 6-fold greater α-synuclein burden in the motor cortex than DLB-DLBD.**
- Recognizing the nature of underlying pathologic processes in patients with CBS due to DLBD is challenging, since there are no biofluid or neuroimaging biomarkers for α-synuclein pathology. **Of the clinical manifestations noted in our cases,** those consistent with CBS lack specificity and are comparable to those observed in CBS due to other pathologic processes.
- **Possible clues to underlying Lewy-related pathology in CBS are features often found in DLB, such as dream enactment behavior consistent with RBD, visual hallucinations, fluctuations in consciousness, systematized delusions and anosmia (Table 1). The relatively good responsiveness to levodopa, as well as hypersensitivity to dopaminergic agonists, also might be clues to Lewy-related pathology,** which contrasts with low frequency of RBD and poor levodopa responsiveness in a clinicopathologic study of CBD.

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