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Corticobasal syndrome with visual hallucinations and probable REM-sleep behavior disorder: an autopsied case report of a patient with CBD and LBD pathology

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Abstract

Corticobasal syndrome and dementia with Lewy bodies are clinical presentations with unique and overlapping features but distinct pathological substrates. We report the case of an 80 year-old man who presented with apraxia, rigidity, slowness, right arm myoclonus, a 10-year history of probable REM-sleep behavior disorder, and later developed visual hallucinations. At autopsy, he had pathological features of corticobasal degeneration, and Lewy body disease confined to the brainstem. This report highlights the importance of considering co-existing pathologies when a clinical presentation defies categorization, and demonstrates that salient features of dementia with Lewy bodies may result from pathology limited to the brainstem.

Keywords

Corticobasal syndrome; corticobasal degeneration; α-synuclein; tau; dementia with Lewy body disease; pathology

Introduction

The term corticobasal syndrome (CBS) acknowledges that not all patients who present with an asymmetric akinetic-rigid syndrome accompanied by variable admixtures of tremor, cortical sensory loss, apraxia, myoclonus, and alien limb phenomena, have underlying corticobasal degeneration (CBD) pathology (Boeve, Lang, & Litvan, 2003; Gibb, Luthert, & Marsden, 1989; Kompoliti et al., 1998). Criteria for diagnosing probable clinical CBS require an asymmetric presentation of two of: limb rigidity, limb dystonia, limb myoclonus as well as two of: orobuccal or limb apraxia, cortical sensory deficit, alien limb syndrome (Table 1) (Armstrong et al., 2013). CBD is a 4-repeat (4-R) tauopathy characterized by tau-immunoreactive ballooned neurons, astrocytic plaques, coiled bodies, and teeming subcortical white matter threads (Gibb et al., 1989; Gibb, Luthert, & Marsden, 1990; Houlden et al., 2001; Komori, 1999). Studying patients with CBS has revealed a range of

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underlying non-CBD pathologies, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), FTLD-TDP Type A, Lewy body disease (LBD), and even Creutzfeldt-Jakob disease (CJD) (Boeve et al., 2003; Josephs et al., 2010; Lee et al., 2011).

Dementia with Lewy bodies (DLB) is also a mixed term containing clinical ("dementia") and pathological "Lewy bodies" annotations, introduced in 1996 to describe older patients with dementia and neuropathological findings of Lewy bodies, which may occur in the brainstem only, ascend to include limbic stuctures ("transitional limbic"), or reach all the way to the neocortex ("diffuse neocortical")(McKeith, 2006; McKeith et al., 2017, 1996). Lewy bodies stain with antibodies against α-synuclein, a presynaptic protein that is the hallmark of Lewy body disease spectrum disorders (Spillantini et al., 1997). Prevailing criteria for the clinical diagnosis of probable DLB were updated in 2017 by the 4th consensus report of the DLB consortium and include a progressive cognitive decline interfering with social and occupational functioning and at least two of four core clinical features: fluctuating cognition with variations in attention and alertness, recurrent visual hallucinations, REM sleep behavior disorder, and parkinsonism. Alternatively, probable DLB can be diagnosed with one core feature and at least one indicative biomarker such as reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET, abnormal 123iodine-MIBG myocardial scintigraphy, and polysomnographic confirmation of REM sleep without atonia (Table 1) (McKeith et al., 2017). To help disambiguate the clinical from pathological terms, throughout we use DLB when referring to the clinical syndrome and LBD when referring to the neuropathological diagnosis. Neuropathological criteria recognize three stages of LBD: brainstem predominant, transitional limbic, and diffuse neocortical (Kosaka, Yoshimura, Ikeda, & Budka, 1984). It is often assumed that the cardinal symptoms of DLB, such as visual hallucinations and proneness to delirium, do not emerge until Lewy bodies reach the limbic structures or even association cortex (Ishii et al., 1998; Nagahama, Okina, Suzuki, & Matsuda, 2010; Perneczky et al., 2008; Sanchez-Castaneda et al., 2010).

In this report, we describe the longitudinal clinical and imaging features of a patient with clinical features of CBS and DLB. Autopsy revealed CBD and LBD pathology, each of which could explain key aspects of the clinical syndrome. This case highlights the importance of considering two or more pathological conditions when the clinical features span two or more clinical syndromes.

Materials and methods

Subjects

The patient presented at the age of 80 years and was followed for three years at the University of California, San Francisco (UCSF). Thirty healthy older men matched for age (mean = 76.8, standard deviation (SD) = 4.2), education (mean = 16.8, SD = 1.7) and handedness (right handed) served as a control group for the interpretation of neuropsychological test results (Table 2). All control group participants received a semi-structured history and physical examination by a behavioral neurologist and a standardized battery of cognitive tests administered by a neuropsychologist (Kramer et al., 2003). They were screened as clinically normal by consensus at a multidisciplinary case conference. All

subjects (or their surrogates) provided written informed consent prior to participation. The University of California, San Francisco's Committee on Human Research approved the study.

Neuropsychological testing

In addition to a full neurological examination, a neuropsychological battery, described elsewhere (Kramer et al., 2003), was administered on each of the three visits. Various aspects of cognition were assessed, including general mental status, memory, language, visuospatial functioning, and executive functioning abilities. Mood was assessed using the geriatric depression scale (GDS).

Neuroimaging

A clinical MRI scan performed on a 1.5 Tesla scanner was obtained following the first visit, including sagittal T1 and coronal FLAIR sequences.

Neuropathology

The fresh brain was cut into ~1-cm thick coronal slabs, which were alternately fixed in 10% neutral buffered formalin for 72 hours or rapidly frozen. Because the patient had predominantly right sided motor symptoms, the left brain was utilized for microscopic examination. Basic and immunohistochemical stains were applied to 8 μm thick sections cut from 25 paraffin-embedded tissue blocks dissected from the fixed slabs, covering dementia-related regions of interest and following standard diagnostic procedures (Hyman & Trojanowski, 1997). Immunohistochemistry was performed using antibodies to: TDP-43 (1:2000, Proteintech Group, Chicago, IL, USA), hyperphosphorylated tau (CP-13 antibody, courtesy of P. Davies, NY), beta-amyloid (4G8, 1:250, Millipore, Billerica, MA, USA), alpha synuclein (1:1000, syn211, 36–008, Millipore, Billerica, MA, USA). For all antibodies, immunoperoxidase staining was performed using an avidin-biotin complex detection system (Vectastain ABC kit; Vector Laboratories, Burlingame, CA,USA) with 3,3 diaminobenzidine as the chromogen. Slides were pretreated for antigen retrieval by immersion in citrate pH 6.0 in an autoclave at 121°C for 5 min. The primary antibodies were incubated overnight at 4°C and species-specific biotinylated secondary antibodies were incubated for one hour at room temperature. All immunohistochemical runs included positive control sections to exclude technical factors as a cause of absent immunoreactivity.

Results

Clinical history

The patient was an 80 year old right-handed man referred in 2005 for jerking movements in his hands. He was a World War II veteran and worked as a highway patrolman for most of his life. He was described as a "handyman" who enjoyed restoring antique furniture. His clinical history unfolded over the course of fourteen years, as follows.

Roughly 10 years prior to presentation, in 1995, he began acting out vivid dreams, which often featured combat scenarios. He would often scream out, fight, pull his wife's hair, or kick or punch her side while dreaming. He did not snore.

His first motor symptom arose in 2002, when he began having difficulties with fine motor skills. For example, he struggled to make a turkey truss as he had done during previous holiday seasons. He developed progressive difficulty manipulating screwdrivers and other tools.

In 2003, writing became impaired secondary to tremor and jerky movements in his right hand. He was no longer able to sign checks and switched most of his dexterous activities to his left hand. In 2004, he stopped driving due to the subjective feeling of slowed reflexes. He manipulated objects incorrectly, such as using the knife handle to spread cheese on a cracker or holding a screwdriver upside down. He had difficulties buttoning his shirt but lacked undoing or intermanual conflict phenomena. Visuospatial skills also declined that year. For example, he once placed a hot dog perpendicularly on a bun.

Upon presentation in 2005, his gait was limited by osteoarthritis of the knees. His language skills, memory, executive functions and behavior were spared, and mild depression was reported. His initial Clinical Dementia Rating (CDR) scale total score was 0.5, and his wife endorsed depression and sleep disturbances on the Neuropsychiatric Inventory (NPI).

His past medical history was not contributory. His family history was unremarkable, lacking relatives with parkinsonism or dementia. On initial neurological examination in 2005, he was alert, well-groomed, and cooperative, with normal affect. He was mildly stimulus-bound and imitative. Speech was slow and hypophonic with no orobuccolingual or speech apraxia. He had significant ideomotor limb apraxia in both upper and lower limbs bilaterally. He had full visual fields and normal pursuits and saccades. There was mild masking of facies. The tongue did not fasciculate. Motor examination revealed mildly increased tone in the upper limbs with right arm cogwheeling during activation of the left. He had an intermittent and stimulus-sensitive myoclonus bilaterally, worse on the right side. There was a subtle resting tremor on the right, with a more prominent action tremor. Repetitive hand, finger and foot movements were slowed and had low amplitude. Sensory examination revealed a mild decrease in vibratory sense in the feet bilaterally with bilateral agraphesthesia in the hands. His right hand drifted up and sideways when his arms were extended with eyes closed. Reflexes were normal. Dysmetria was absent. Gait was slightly wide-based and antalgic.

One month after initial evaluation, the patient reported the sensation of a presence with him, which he described as “reminiscent of a ghost,” or a “shadow trying to pass [him] on the left side.” In addition, he experienced the visual hallucination of a child wearing a green sweater. He reported visual misperceptions. Spots of dirt and dust on surfaces appeared to gyrate and move like spiders. A striped pattern on his wife’s sweater was perceived as a streak of talcum powder. These occurred in the absence of any dopaminergic agent. His examination was unchanged and he was prescribed donepezil. Four months later, visual hallucinations and dream enactment had diminished. Examination revealed worsening motor findings, as well as delayed saccade initiation to the left and impaired leftward optokinetic reflexes.

In 2006, he underwent a left total knee replacement. His post-operative course was complicated by an episode of in-hospital delirium during which he became agitated (removing cardiac leads and pulling intravenous lines), and hallucinatory, alternating with

extreme somnolence. Six months later, after a protracted recovery, motor symptoms worsened and he became more apathetic. His arousal level fluctuated, and he was taken to the emergency room several times for unresponsiveness; several hours later he would awaken and ask to be taken home. His gait became more stooped, and mild retro-pulsive instability was noted.

Additional decline occurred in 2007 in the following areas: gait, motor function (left hand significantly more affected and right almost immobile), speech (faltering with decreased fluency), and visuospatial skills (two falls when trying to sit at the edge of the bed and misjudging distance). Physical exam revealed word-finding pauses, right-left confusion, acalculia, delayed saccade initiation, worsening bradykinesia, and diffuse multifocal myoclonus. CDR total score was 1. Levodopa/ carbidopa therapy was tried for two months without success and with reported worsening of his tremor. Visual hallucinations did not worsen at this point and he was already on cholinesterase inhibitors.

Swallowing difficulties emerged in 2008, and he had episodes of aspiration pneumonia with multiple inpatient hospital admissions. He was moved to a residential care facility, developed another episode of aspiration pneumonia, and transferred to a hospice program. He passed away in 2009, seven years after his first clinical motor symptom.

Neuropsychological testing

Neuropsychological evaluations conducted at the initial visit and two follow-up visits are presented in Table 2. Initial testing indicated deficits in episodic memory, figure copy and executive functions, with relative sparing of language and spatial perception. Follow-up evaluations revealed greater motor difficulties and worsening of visuospatial perception and syntax comprehension, a decline in visual memory, with no significant decline in verbal memory which remained poor. Significant depressive symptomatology was endorsed throughout.

Neuroimaging

Brain MRI was performed at an outside facility one month after the patient's presentation to UCSF (Figure 1) and revealed dorsal frontoparietal and perirolandic atrophy, extending posteriorly into the superior and inferior parietal lobules, worse on the left than the right. Mild left hippocampal volume loss was noted. Few, small and bilateral T2 and FLAIR hyperintense lesions were noted in the subcortical and periventricular white matter.

Neuropathology

The fresh brain weighed 1300 grams. Gross examination revealed mild to moderate posterior dorsal frontal atrophy and severe dorsal anterior parietal atrophy involving the superior parietal lobules. Atrophy was worse on the left side (Figure 1). The substantia nigra was moderately depigmented. On microscopic examination, moderate to severe microvacuolation and astrogliosis were seen in the precentral gyrus, superior frontal sulcus, subgenual cingulate cortex, putamen, amygdala, CA1/subiculum subregions of the hippocampus (where there was nearly complete neuronal loss), locus ceruleus, and dorsal motor nucleus of the vagus (Table 3). The neuronal loss in CA1/subiculum was sufficient for a diagnosis of

hippocampal sclerosis. Hematoxylin and eosin (H&E) staining revealed scattered pale bodies in substantia nigra but no definite Lewy bodies.

Immunohistochemistry for beta-amyloid revealed sparse diffuse plaques in the angular gyrus and middle frontal gyrus, with scattered neuritic plaques in angular gyrus . Mild cerebral amyloid angiopathy was found in angular gyrus and calcarine cortex.

In affected regions, immunohistochemistry for hyperphosphorylated tau revealed numerous neuronal cytoplasmic inclusions (NCIs), with ballooned neurons in cortical layer 5 (Figure 2; Table 3). Astrocytic plaques and neuropil threads were abundant in a similar cortical distribution to NCIs. Numerous thorny astrocytes were found in globus pallidus and were scattered throughout other cortical, subcortical, and limbic structures. Teeming white matter threads and coiled oligodendroglial inclusions were observed subjacent to affected cortices. The abundance of tau pathology generally correlated with the severity of microvacuolation and astrogliosis. These findings provided unequivocal evidence of CBD (Gibb et al., 1989, 1990).

Immunohistochemistry for alpha synuclein showed frequent Lewy bodies in the dorsal motor nucleus of the vagus (Figure 3; Table 3) and sparse Lewy bodies in substantia nigra, locus ceruleus and nucleus of the solitary tract. No Lewy bodies were found in other regions examined (Table 3) including the anterior cingulate cortex, middle frontal gyrus, precentral gyrus, post central gyrus, amygdala, superior frontal sulcus, dentate gyrus, the hippocampus, entorhinal cortex, angular gyrus, and occipital striate cortex. Abundant Lewy neurites were seen in dorsal raphe and dorsal motor nucleus of the vagus, with moderate numbers in substantia nigra, tectum, periaqueductal gray, locus ceruleus and median raphe and small numbers in the central nucleus of the amygdala and nucleus of the solitary tract, corresponding to a brainstem predominant LBD (McKeith et al., 2005) with a Braak PD stage of 3 (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004). No Lewy neurites were found in other regions examined (Table 3).

TDP-43 immunohistochemistry revealed a few neuronal cytoplasmic inclusions in the dentate gyrus and CA1/subiculum. These inclusions were more frequent in the amygdala, and the amygdala and CA1/subiculum also contained neuropil threads and glial cytoplasmic inclusions. TDP-43 also laced some short annular astroglial processes (Figure 2) in several regions, suggesting colocalization with tau-immunoreactive astrocytic plaques, as has been previously described (Uryu et al., 2008; Yokota et al., 2010).

Discussion

The patient suffered from a progressive neurodegenerative disease with clinical features of CBS and DLB. His clinical presentation met the diagnostic criteria for probable CBS: unilateral limb rigidity, myoclonus, limb apraxia and cortical sensory deficits (Armstrong et al., 2013). The distribution of his CBD pathology in perirolandic cortex, basal ganglia, and mid-brain, accounts for most or all of his clinical motor symptoms.

In rare cases, LBD with severe burden of Lewy pathology in the peri-rolandic regions may present as CBS, however our patient’s LBD pathology was confined to the brainstem

(Kasanuki et al., 2018). His early symptoms of probable REM-sleep behavior disorder (RBD) may have been the first indicator that LBD pathology was also present. RBD has been tightly linked to underlying α-synuclein pathology (Boeve, Silber, Ferman, Lucas, & Parisi, 2001; Boeve et al., 2003; Molano et al., 2010), and idiopathic RBD has been proposed as an early stage of Parkinson's disease (Ellmore et al., 2010) and its presence increases the likelihood that DLB is accompanied by LBD pathology (Ferman et al., 2011). RBD is rare in pure tauopathies and has been reported in less than 5% of CBS cases (Cooper & Josephs, 2009). No previous reports have described RBD in autopsy-proven CBD. RBD has been described only in one case of autopsy-proven PSP severely involving the brainstem nuclei (Compta, Marti, Rey, & Ezquerra, 2009); however, even if RBD could be found in tau pathology that severely affects the brainstem, our patient's predominant pathology in the brainstem was LBD. The patient's later development of visual hallucinations, feeling of a presence akin to the extracampine hallucination, fluctuations in sensorium, and hypersensitivity to CNS agents further substantiated a clinical diagnosis of probable DLB.

Many authors have suggested that LBD-associated visual hallucinations arise due to amygdala or cortical Lewy body pathology and associated neurodegeneration (Harding, Broe, & Halliday, 2002; Harding, Stimson, Henderson, & Halliday, 2002; Kasanuki et al., 2012; Papapetropoulos, McCorquodale, Gonzalez, Jean-Gilles, & Mash, 2006; Selikhova et al., 2009). Neuroimaging studies have pointed to parieto-occipito-temporal hypoperfusion/hypometabolism as the strongest correlate and have implied that the imaging findings result from local pathology rather than indirect effects of damage elsewhere (Ishii et al., 1998; Nagahama et al., 2010; Perneczky et al., 2008; Sanchez-Castaneda et al., 2010). Moreover, a cholinergic deficit of the occipito-temporal cortices was also proposed as contributing to the neurophysiology of visual hallucinations in patients with DLB (Ballard et al., 2000; O'Brien et al., 2008; Perry et al., 1990). Our patient's complete lack of cortical Lewy body pathology suggests that his, and likely others', salient clinical DLB features (visual hallucinations, fluctuations in sensorium, neuroleptic sensitivity, and RBD) may be explained by α-synuclein pathology confined to the brainstem. Although it remains conceivable that his hallucinations were caused by cortical CBD pathology, visual hallucinations have been reported in only 7% of patients with pathologically proven CBD (Lee et al., 2011) and 5% of patients with clinical CBS (Cooper & Josephs, 2009).

TDP-43 pathology has been shown to co-occur with CBD in up to 17% of cases (Uryu et al., 2008; Yokota et al., 2010) and usually consists of TDP-43-positive neuronal cytoplasmic inclusions in the dentate gyrus granule cells, entorhinal cortex and temporal and frontal cortices, as well as many threadlike TDP-43 positive inclusions that resemble astrocytic plaques and overlap with tau pathology. The clinical significance of the TDP-43 pathology colocalizing with the tau astrocytic plaques is unclear (Uryu et al., 2008). In addition, this patient had TDP-43 pathology associated with hippocampal sclerosis, which may have accounted for his episodic memory deficits on neuropsychological testing. The clinical significance of the patients amygdala TDP-43 pathology remains unclear given the high prevalence of this finding in cognitively normal older subjects (Wilson et al., 2013).

A limitation to understanding the clinical correlation of the pathological changes in this case include the retrospective nature of collecting data through a chart review.

Conclusions

Co-occurring, clinically significant CBD-LBD pathology presents a major diagnostic challenge. Although LBD and AD often co-occur and may have synergistic effects, the admixture of CBD and LBD provides a rare and unique window into the clinicopathological correlations of both disorders. The present findings further emphasize that typical features of two underlying pathologies need not be forced into a single clinical diagnosis. The rule of diagnostic parsimony often induces clinicians to bend their diagnostic boundaries, but clinical features strongly suggestive of a given disease other than the leading diagnosis should lead clinicians to consider mixed pathology, especially in older patients.

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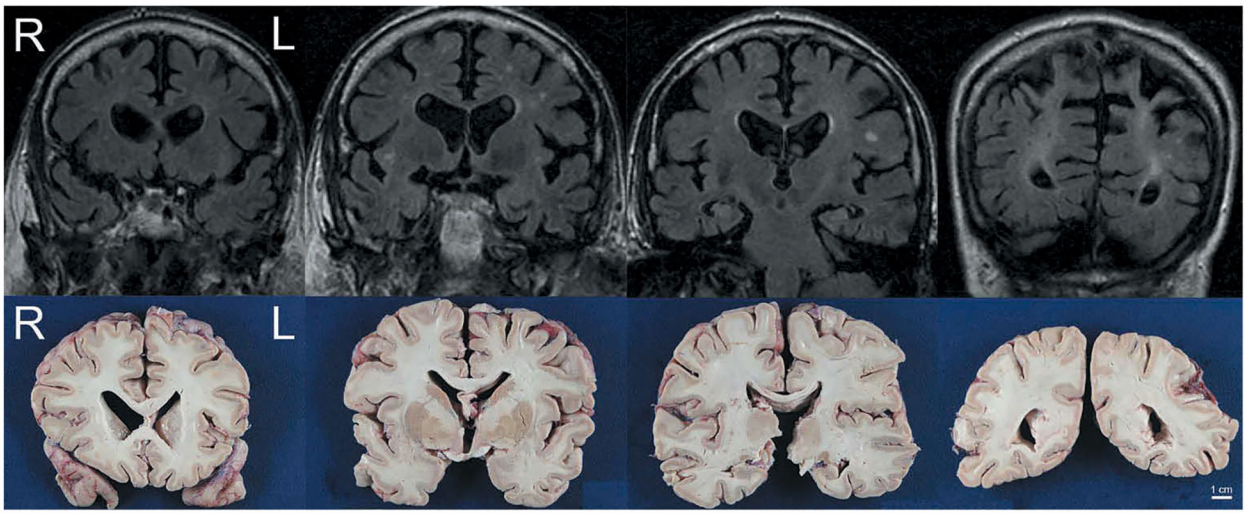

Figure 1.

Top: Coronal FLAIR images ordered antero-posteriorly from left to right show parenchymal volume loss in the left dorsal frontal lobe, superior parietal lobule, and left hippocampus, more prominent on the left; *Bottom*: Gross examination of coronal post-mortem slabs showing atrophy in the superior parietal lobule, worse on the left side.

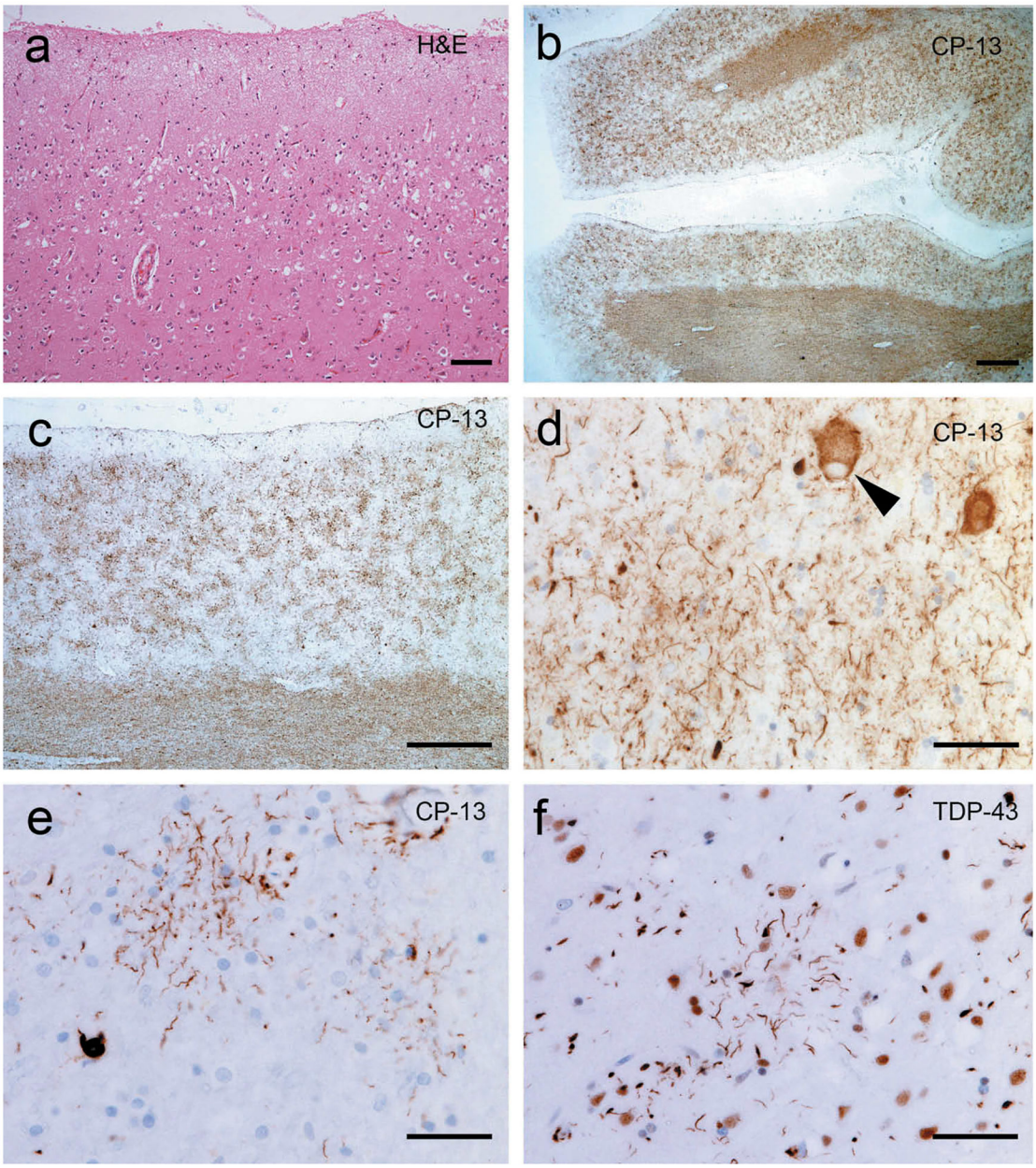

Figure 2.

(a) Hematoxylin and eosin staining of superior parietal lobule showing microvacuolation and astrogliosis. (b-e) Immunohistochemical staining for hyperphosphorylated tau (CP-13 antibody) in superior parietal lobule revealed numerous neurofibrillary tangles (NFTs) and neuronal cytoplasmic inclusions (NCIs). Ballooned neurons identified in layer 5 (d, arrowhead) in precentral gyrus. Astrocytic plaques and neuropil threads were widespread (e). (f) TDP-43 immunohistochemistry showed immunoreactivity in astroglial processes that appeared to lace the astrocytic plaques observed with tau immunohistochemistry. Scale bar in (a) represents 100 μm, in (b) represents 1000 μm, in (c) represents 500 μm and in (d, e, f) represents 50 μm.

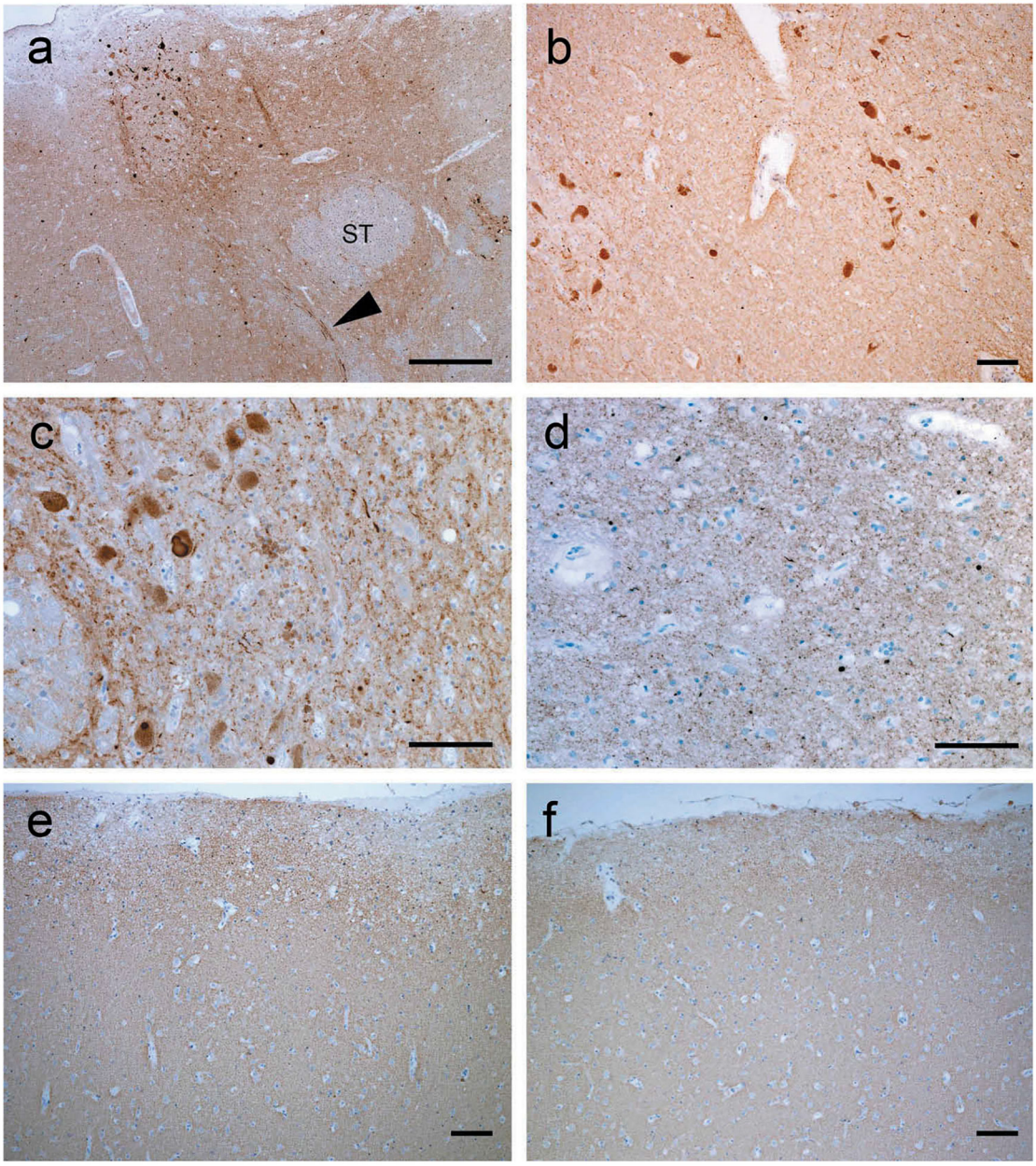

Figure 3.

Alpha synuclein immunohistochemistry. (a) Large numbers of Lewy bodies in the dorsal motor nucleus of the vagus and Lewy neurites in its exiting fibers (arrowhead). ST = solitary tract). (b-c) Lewy bodies and Lewy neurites in the substantia nigra. Minimal Lewy pathology was found in amygdala (d), and none was observed in entorhinal cortex (e) or anterior cingulate cortex (f). Scale bar in (a) represents 1000 μm, in (b-f) represents 100 μm.

Table 1.

Diagnostic criteria for CBS and DLB, as well as patient's symptoms that fulfill these criteria.

	Corticobasal syndrome	**Dementia with Lewy bodies**
Consensus Criteria	Two of: **1** Limb rigidity **2** Limb dystonia **3** Limb myoclonus **And** two of: **1** Orobuccal or limb apraxia **2** Cortical sensory deficit **3** Alien limb syndrome	Two of: **1** Fluctuating cognition **2** Visual hallucinations **3** RBD **4** Parkinsonism **Or** one of above plus one of: **1** Reduced dopamine transporter uptake in basal ganglia by SPECT or PET **2** Abnormal 123iodine-MIBG myocardial scintigraphy **3** Polysomnographic confirmation of REM sleep without atonia
Patient symptoms	Unilateral limb rigidity Limb myoclonus Limb apraxia Cortical sensory loss	Fluctuating cognition Visual hallucinations Probable RBD

MIBG: Meta-iodobenzylguanidine, PET: positron-emission tomography, RBD: REM-sleep behavior disorder, REM: Rapid eye movement, SPECT: Single-photon emission computed tomography.

Table 2.

Neuropsychological evaluation results at initial visit and two follow up visits compared to controls.

		Patient's evaluation results		
Test (maximal score)	**Controls (n = 30)**	**Evaluation I Time 0**	**Evaluation II 10 months**	**Evaluation III 22 months**
CDR	0.1 (0.2)	0.5	0.5	1
MMSE (30)	28.2 (1.4)	23**	21**	23**
Memory				
9-item CVLT learning trials (9, 9, 9, 9)	5,6,7,8	3, 4, 4, 6*	2, 4, 5, 5*	3, 5, 4, 5*
9-item CVLT total across learning trials	26.5 (4)	17*	16**	17*
9-item CVLT 30 second recall (9)	6.7 (1.6)	4*	5	4*
9-item CVLT ten minute recall (9)	6.4 (2)	3*	3*	4
9-item CVLT recognition (9)	8.5 (0.8)	6**	8	6**
9-item CVLT recognition false positives	0.7 (1.1)	1	2	7**
Benson figure delayed recall (17)	11.4 (3)	4*	NA	NA
Language				
15-item Boston Naming Test (15)	14.2 (1.2)	14	15	13
Syntax comprehension (5)	4.8 (0.4)	4*	4*	2**
Visuospatial				
Benson figure copy (17)	15.2 (1.3)	9**	NA	NA
VOSP number location (10)	9.1 (1.1)	8	8	6**
Arithmetic problem solving (5)	4.7 (0.7)	4	3**	NA
Executive Functions				
Modified Trails: correct within 120 ' (14)	14 (0)	1**	1**	NA
Category Fluency (Animals)	19.3 (4.1)	13*	12*	11*
Letter Fluency (D words)	14.6 (4.4)	3**	5*	3**
Stroop Interference: correct within 60 '	44.6 (9.9)	15**	15**	NA
Digits Backward (Max span)	5.3 (1.3)	3*	NA	NA
Geriatric Depression Scale-self report (30)	2.4 (2.1)	14**	14**	14**

CDR = Clinical Dementia Rating; CVLT = California Verbal Learning Test; MMSE = Mini Mental State Examination; Modified Trails = Trail Making of numbers and days of the week; VOSP = Visual Object and Space Perception Battery

*Low performance (−2.5 < z-score < −1.5)

**Extremely low performance (z-score < −2.5)

Scores not marked are within average range

Table 3.

Semi-quantitative ratings of microvacuolation, gliosis, tau, α-synuclein and TDP-43 pathology.

	H&E		Tau					α-synuclein		TDP-43	
	Microvacuolation	**Astrogliosis**	**NFT**	**NCI**	**WMT**	**AP**	**NT**	**Lewy bodies**	**Lewy neurites**	**NCI**	**GCI**
Subgenual ACC	++	+++	0	++	+++	+++	0	0	0	N/A	N/A
Pregenual ACC	+	+	0	++	+++	+++	0	0	0	N/A	N/A
Middle frontal gyrus	+	+	0	++	++	+++	0	0	0	N/A	N/A
SFS	++	++	0	+++	+++	++	0	0	0	0	+++
Middle insula	+	+	0	+++	+++	+++	0	N/A	N/A	N/A	N/A
Precentral gyrus	++	++	0	+++	+++	++	0	0	0	N/A	N/A
Entorhinal cortex	0	0	+++	++	++	++	++	0	0	0	0
ITG	+	+	+++	+++	+++	++	++	N/A	N/A	0	+
SPL	N/A	N/A	0	+++	+++	+++	0	0	0	0	+++
Angular gyrus	0	+	0	+	+	++	0	N/A	N/A	N/A	N/A
Amygdala	N/A	++	N/A	N/A	N/A	N/A	N/A	0	+	+++	+
Dentate gyrus	N/A	0	+++	0	0	0	0	0	0	+	0
CA3–4	N/A	0	+	0	0	+	0	0	0	0	0
CA2	N/A	0	+	0	0	+	0	0	0	0	0
CAI/subiculum	N/A	+++	++	0	+++	+	+	N/A	N/A	+	+
Putamen	N/A	++	0	++	++	++	0	N/A	N/A	N/A	N/A
Globus Pallidus	N/A	+	0	+++	+++	++	0	N/A	N/A	N/A	N/A
Claustrum	N/A	+	0	+++	0	++	0	N/A	N/A	N/A	N/A
Substantia Nigra	N/A	+	0	+++	0	0	++	+	++	0	0
III Nucleus	N/A	0	0	++	0	0	++	0	+++	0	0
Locus ceruleus	N/A	++	N/A	N/A	N/A	N/A	N/A	+	++	N/A	N/A
DMN-X	N/A	++	N/A	N/A	N/A	N/A	N/A	+++	+++	N/A	N/A

All regions examined are in the left hemisphere, H&E: Hematoxylin & Eosin, NFT: Neurofibrillary tangles, NCI: neuronal cytoplasmic inclusions, WMT: white matter threads, AP: Astrocytic plaques, NT: Neuropil threads, GCI: Glial cytoplasmic inclusions, ACC: anterior cingular cortex, DLPC: dorsolateral prefrontal cortex, SFS: Superior frontal sulcus, ITG: Inferior temporal gyrus, SPL: Superior parietal lobule, DMN-X: Dorsal motor nucleus of cranial nerve X, + mild, ++ moderate, +++ severe, 0 none, N/A Not assessed.