Corticobasal degeneration

Gerard M. Saranza[1], Jennifer L. Whitwell[2], Gabor G. Kovacs[1,3,4,5] and Anthony E. Lang*[,1,5]

[1]Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada
[2]Department of Radiology, Mayo Clinic, Rochester, Minnesota, United States
[3]Tanz Centre for Research in Neurodegenerative Disease and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
[4]Laboratory Medicine Program, University Health Network, Toronto, Ontario, Canada
[5]Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
*Corresponding author: E-mail: Anthony.Lang@uhnresearch.ca

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International Review of Neurobiology, Volume 149
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2019.10.014

Abstract

Corticobasal degeneration (CBD) is a rare neurodegenerative disease characterized by the predominance of pathological 4 repeat tau deposition in various cell types and anatomical regions. Corticobasal syndrome (CBS) is one of the clinical phenotypes associated with CBD pathology, manifesting as a progressive asymmetric akinetic-rigid, poorly levodopa-responsive parkinsonism, with cerebral cortical dysfunction. CBD can manifest as several clinical phenotypes, and similarly, CBS can also have a pathologic diagnosis other than CBD. This chapter discusses the clinical manifestations of pathologically confirmed CBD cases, the current diagnostic criteria, as well as the pathologic and neuroimaging findings of CBD/CBS. At present, therapeutic options for CBD remain symptomatic. Further research is needed to improve the clinical diagnosis of CBD, as well as studies on disease-modifying therapies for this relentlessly progressive neurodegenerative disorder.

1. History

In 1967 and 1968, Rebeiz, Kolodny and Richardson described three cases with abnormalities in motor control and posture, which they called corticonigral degeneration with neuronal achromasia based on the pathologic findings of asymmetrical frontoparietal cortical atrophy, loss of neurons in the substantia nigra and swollen neurons (achromatic cells) (Rebeiz, Kolodny, & Richardson, 1967, 1968). Gibb and colleagues first used Corticobasal degeneration (CBD) in 1989 (Gibb, Luthert, & Marsden, 1989). Following the description of additional cases (Riley et al., 1990; Rinne et al., 1994), further characterization of CBD as an entity occurred with the introduction of immunostaining for tau, Gallyas silver staining, and with the biochemical and ultrastructural characterization of tau. (Feany & Dickson, 1995; Feany et al., 1995; Horoupian & Chu, 1994; Ksiezak-Reding et al., 1994; Mori, Nishimura, Namba, & Oda, 1994; Uchihara et al., 1994; Wakabayashi et al., 1994). Soon the spectrum of clinical phenotypes

associated with CBD pathology was expanded. Finally, propagation of tau pathology inoculated from human CBD cases into experimental animal models opened new avenues for research and therapy development (Boluda et al., 2015; Clavaguera et al., 2013).

2. Definition and pathology

2.1 Definition

CBD is a neuropathological term to define a neurodegenerative disease characterized by the predominance of pathological tau deposition in various cell types and anatomical regions (Kovacs, 2015). Corticobasal syndrome (CBS) is the term used to describe one of the characteristic clinical syndromes associated with CBD pathology (Boeve, Lang, & Litvan, 2003; Doran et al., 2003). The distribution of neuronal loss and tau pathologies determines the clinical presentation. Accordingly, a wide range of clinical symptoms are associated with CBD pathology, and similarly, CBS is associated with other neuropathologies (Ling et al., 2010b). CBD is relatively rare, but accurate epidemiologic studies with pathologic confirmation are lacking. A recent study, which used only clinical diagnostic criteria, showed a pooled prevalence of frontotemporal lobar degeneration (FTLD), CBS, and progressive supranuclear palsy (PSP) of 10.6/100,000/year (Coyle-Gilchrist et al., 2016). CBD has been detected in community-based aging studies suggesting an even higher incidence in the elderly population, which might go underrecognized (Kovacs et al., 2013).

2.2 Classic neuropathological features

Macroscopic evaluation of the brain reveals focal and asymmetric cortical atrophy mostly in the superior frontal or parietal parasagittal regions. The pre- and postcentral regions may also be affected. The occipital lobe is atrophic in rare cases with posterior cortical atrophy (PCA), and prominent FTLD is seen in some cases. The degeneration of the basal ganglia is represented by the atrophy and flattening of the caudate nucleus. The subthalamic nucleus is preserved, and the brainstem is not characteristically atrophic. The substantia nigra shows depigmentation in cases with motor symptoms but may appear relatively preserved in those with predominant cognitive decline.

Classic histopathological features comprise neuronal loss and gliosis in atrophic cortical and subcortical areas, including the substantia nigra when

motor symptoms are present. Swollen neurons without visible Nissl substance and with an eccentric nucleus (indistinguishable from Pick cells in Pick's disease), termed ballooned achromatic neurons, are one important histological hallmark. They are commonly seen in the affected cortices. Neither the ballooned neurons nor the frequently seen microvacuolation of the superficial cortical layers are specific for CBD as these can be seen in other disorders (Dickson, 1999).

2.3 Biochemistry and immunostaining for tau

CBD belongs to the group of primary tauopathies. Based on the distinct involvement of anatomical areas, cell types, and the presence of distinct isoforms of tau in the pathological deposits, several neuropathological phenotypes are distinguished (Kovacs, 2015). Tau isoforms are generated by the alternative splicing of exons 2, 3, and 10 of the *MAPT* (microtubule-associated protein tau) gene. Tauopathies are distinguished based on the ratio of 3 repeat (R)- and 4R-tau and two or three major phospho-tau bands (60, 64, and 68 kDa) in Western blot of sarkosyl-insoluble fractions (Lee, Goedert, & Trojanowski, 2001; Sergeant, Delacourte, & Buee, 2005; Spillantini & Goedert, 2013).

Based on a similar biochemical pattern, CBD belongs to the group of 4R tauopathies, which further include progressive supranuclear palsy (PSP), argyrophilic grain disease (AGD) and globular glial tauopathies (GGT) (Kovacs, 2015). A study comparing immunoblotting patterns seen in PSP and CBD demonstrated that a 33 kDa band predominated in the low molecular weight tau fragments in PSP, whereas two closely related bands of approximately 37 kDa predominated in CBD, suggesting different proteolytic processing of abnormal tau in PSP and CBD (Arai et al., 2004). A recent study extended these findings, indicating that the differences may be related to the protease resistance of pathological tau proteins (Taniguchi-Watanabe et al., 2016). On analysis of sarkosyl-insoluble tau banding patterns using antibodies against tau C-terminus, tauopathies can be biochemically classifiable into at least four types, including Pick's disease (PiD), PSP, CBD and Alzheimer's disease (AD) (Taniguchi-Watanabe et al., 2016).

Neuronal tau pathology in CBD is characterized by diffuse granular cytoplasmic immunoreactivity of neurons, threads, and small spherical cytoplasmic bodies referred to also as corticobasal bodies particularly in the substantia nigra (Fig. 1A and B). In the white matter, prominent accumulation of thread-like structures and coil-like or coma-like intracytoplasmic profiles in oligodendroglia called coiled bodies can be observed (Fig. 1C and D).

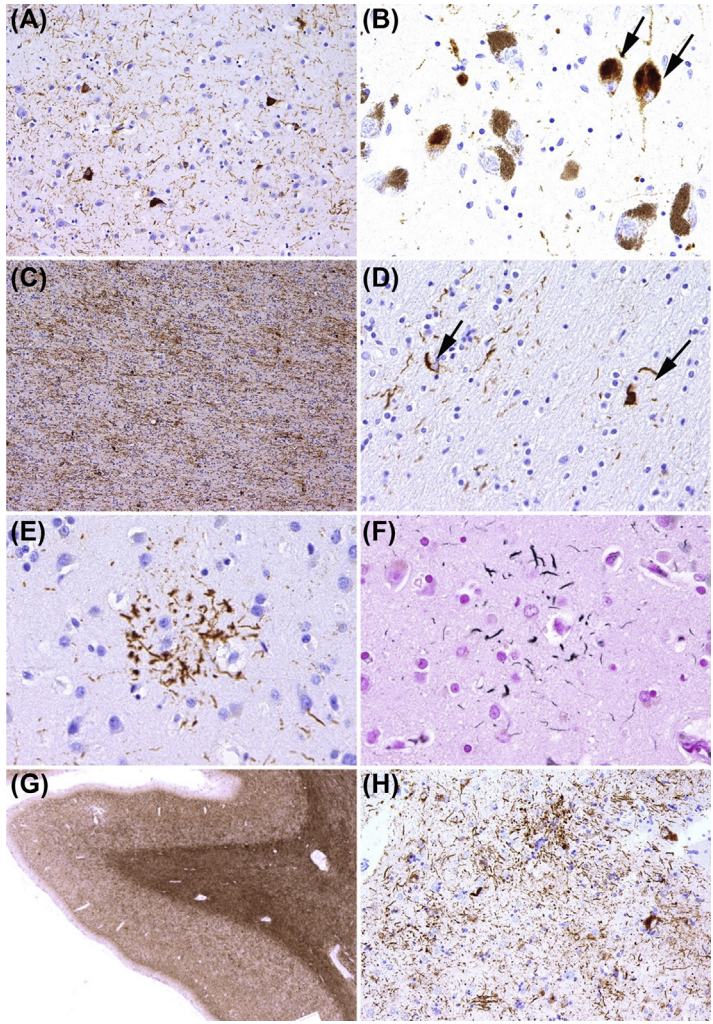

Fig. 1 ***Immunohistochemical findings of CBD.*** (A, B) Neuronal tau pathology, characterized by diffuse neuronal cytoplasmic immunoreactivity and threads in the cortex (A) and the presence of corticobasal bodies in the substantia nigra (B; indicated by arrows). (C, D) Thread-like structures and coil-like or coma-like intracytoplasmic profiles in oligodendroglia called coiled bodies (indicated by arrows) in the white matter. (E, F) Tau positive astrocytic plaque (E) detectable by Gallyas silver staining (F) in the gray matter. (G, H) Neuronal and glial tau pathology in cortical and subcortical areas in advanced CBD.

Ultrastructurally, twisted tubules are observed in oligodendroglial cells (Arima, 2006; Ksiezak-Reding et al., 1994). One most specific finding in CBD brains is the so-called astrocytic plaque seen in the gray matter. These phosphorylated-tau-positive structures are detectable in Gallyas silver staining and are immunoreactive for p62 and 4R-tau (Fig. 1E and F). These should be distinguished from the ramified astrocytes in PiD, globular astroglial inclusions in GGT, granular/fuzzy astrocytes of AGD, and in particular from tufted astrocytes that characterize PSP along with globose tangles. Tufted astrocytes are represented by star-like tufts of densely packed fibers in the proximal segment of astrocytic processes (Kovacs, 2015). Astrocytic plaques are identified as an annular cluster of short stubby processes representing the distal segment of astrocytic processes (Kovacs, 2015). Evaluation of so-called incidental CBD cases suggests that astrocytic tau pathology in the cortex precedes tau accumulation in neurons, representing one of the first pathological steps in the development of CBD (Ling et al., 2016). This notion has been supported by observations in CBD cases with clinical symptoms and prominent neuronal tau pathology, where tau deposition in astrocytes appears in areas without neuronal tau pathology (Kovacs et al., 2017). A sequential distribution of astrocytic tau pathology can be recognized in CBD, following a predominantly frontal-parietal cortical to temporal-occipital cortical, to subcortical, to brainstem pathway (four stages) with an intracellular maturation of tau deposition beginning with fine granular deposits in astrocytic processes accumulating in the distal segments (Kovacs et al., 2018).

In advanced forms of the disease, massive tau pathology, comprised of a combination of neuronal and glial tau pathology, can be seen in cortical and subcortical areas (Fig. 1G and H). Neuronal and thread-like tau pathology predominate in the cortical areas and adjacent white matter and striatum followed by globus pallidus, thalamus and locus coeruleus. The pontine base may also show tau immunoreactive neurons. Astrocytic plaques are seen mostly in the frontal, motor and parietal cortices, and the striatum. Argyrophilic grains are frequently found in the limbic system (Tatsumi et al., 2014). The distribution of tau pathology shows variability depending on the predominant clinical presentation.

2.4 Concomitant pathologies

Although tau pathology is interpreted as a leading feature, additional neurodegenerative conditions associated with CBD are increasingly recognized. Alpha-synuclein deposition in the form of Lewy body pathology has been

reported in approximately 20% while intermediate to a high level of Alzheimer-related neuropathological change in about 11% of CBD cases (Robinson et al., 2018). TDP-43 is variably reported (15.4%–45%) in CBD (Koga et al., 2018; Robinson et al., 2018; Uryu et al., 2008). Indeed, a recent study indicated that CBD with severe TDP-43 pathology is a distinct clinicopathological entity characterized by PSP-like clinical presentations and severe tau pathology in the olivopontocerebellar system (Koga et al., 2018).

3. Etiology and pathophysiology

3.1 Etiology

Most cases of CBD are idiopathic (sporadic). It is generally considered a sporadic disease, but rare familial, pathologically confirmed cases have been reported (Brown, Lantos, Roques, Fidani, & Rossor, 1996). As for several neurodegenerative conditions, a multifactorial etiology is discussed. There is a lack of evidence for environmental factors for CBD. However, geographical clustering of tauopathies has been described supporting the concept that environmental elements might have relevance for their development (Caparros-Lefebvre et al., 2002; Miklossy et al., 2008).

3.2 Genetics

More than 50 pathogenic mutations of the *MAPT* gene have been identified that are associated with autosomal dominant frontotemporal dementia with parkinsonism, collectively classified as FTDP-17T (Ghetti et al., 2015). In cases with *MAPT* mutations, abnormal accumulation of tau can occur in both neurons and glia. However, certain *MAPT* mutations can result in either clinical phenotypes or pathological features that are indistinguishable from CBS/CBD. These include mutations in exon 10, intron 10, and exon 13 (Forrest et al., 2018; Ghetti et al., 2015). Together with modifying factors that influence pathogenic pathways, *MAPT* mutations lead to dysfunction of the membrane-associated 4R-tau or give rise to increased 4R-tau.

Furthermore, extended tau haplotype (H1) and H1/H1 are also significantly increased in pathologically proven CBD (Houlden et al., 2001). Exploratory genome-wide association studies (GWAS) of 152 pathology confirmed CBD cases showed genetic overlap with PSP and identified SNPs within *MOBP* (myelin-associated oligodendrocyte basic protein) as increasing disease risk (Kouri et al., 2015). Other genes associated with

CBD include a SNP at 8p12, which seems to affect long non-coding RNA kinesin family member 13B (*lnc-KIF13B-1*) (Kouri et al., 2015). A further SNP detected was the chromosome 2p22 locus, which contains the son of sevenless homolog 1 (*SOS1*) (Kouri et al., 2015). Another study revealed shared genetic overlap between CBD and PSP as described at *NSF* (tagging the *MAPT* H1 haplotype), *MOBP*, *CXCR4* (Chemokine receptor encodes a protein important in vascularization and cerebellar development), *EGFR* (encodes epidermal growth factor receptor), and *GLDC* (encodes glycine dehydrogenase) (Yokoyama et al., 2017). These variants were associated with a unique neuroanatomic gene expression signature that may influence regional and neuronal selective vulnerability. Finally, a recent study suggested immune-mediated genetic enrichment in a cohort of FTD-related disorders that included CBD (Broce et al., 2018).

3.3 Pathophysiology

3.3.1 General concepts

Tau dysfunction is thought to be the driving factor in the pathogenesis of CBD as emphasized by the discovery that *MAPT* mutations associated with tau protein dysfunction are sufficient to cause neurodegeneration and dementia (Goedert, 2018). The major driving force for neurodegeneration is thought to be mediated through post-translational modifications of tau such as phosphorylation, acetylation, methylation, glycation, isomerization, O-GlcNAcylation, nitration, sumoylation, truncation, and ubiquitination (Spillantini & Goedert, 2013). In particular, hyperphosphorylation might lead to altered binding affinity and, thus, malfunction of microtubules (i.e., *a loss of function mechanism*). Accumulation of hyperphosphorylated tau in dendritic spines also impairs synaptic function (Frandemiche et al., 2014; Harris et al., 2012).

The assembly of monomeric tau leads to the formation of tau filaments and tau-protein deposits in different cell types. This ordered assembly underlies tau seeding and recruitment of normal tau by pathological tau species leading to aggregate formation made of filaments (Mudher et al., 2017). It is still unclear what triggers tau aggregation. The pathological process of tau aggregation is thought to lead to a *gain of toxic function* paralleled by a loss of physiological functions of tau such as deficient axonal transport altering synaptic functions (Goedert, Eisenberg, & Crowther, 2017). This is supported by observations that overexpression of mutant human tau leads to filament formation and recapitulate pathological and molecular

characteristics of human tauopathies (Goedert, 2016). On the other hand, overexpression of wild-type human tau in mouse brain does not result in the formation of abundant filamentous inclusions (Gotz et al., 1995).

Further aspects of the pathogenesis include the involvement of microglia and astroglia. Although a direct causal link between microglial activation and neurodegeneration cannot be established, greater microglial activation in CBD has been observed, with microglial burden correlating with tau burden (Ishizawa & Dickson, 2001). Since accumulation of pathological tau in astroglia precedes that in neurons, it has been theorized that these tau-positive astrocytes might phagocytize pathological tau derived from the endings of projecting neurons, or this may simply represent local astroglial upregulation of tau as a response to a yet unidentified event (Kovacs et al., 2018; Ling et al., 2016). In experimental studies, the observation of an inverse correlation between neuronal and astrocytic tau pathology was interpreted as support for the transmission of pathological tau seeding from neurons to neighboring astrocytes. Alternatively, astrocytic tau pathology might spread from one astrocyte to another (Narasimhan et al., 2017). Studies in tau transgenic mouse model of astrocytic tau pathologies suggest that this type of pathology contributes to glial degeneration (Higuchi et al., 2002). Interestingly, neuronal degeneration can be detected in the absence of neuronal tau inclusions as a functional consequence of astrocytic tau pathology (Forman, 2005).

The susceptibility loci discovered for CBD in GWAS studies may link to the dysfunction of vesicular trafficking as well as tau phosphorylation (Kouri et al., 2015; Yokoyama et al., 2017). The biological roles of *CXCR4*, *EGFR*, and *GLDC* coupled with their differential expression patterns in the brain support the idea that these genetic risk factors may promote specific neuroanatomical patterns of tauopathy when observed in different combinations (Yokoyama et al., 2017). The association with the MOBP/SLC25A38 locus results in elevated levels of appoptosin, a protein that activates caspase-3 leading to the cleavage and increased aggregation of tau (Zhao et al., 2015).

3.3.2 Propagation of tau pathology

"Prion-like" cell-to-cell spreading of tau has been proposed to explain the propagation of tau pathology, whereby its release is followed by uptake leading to the formation of new aggregates inside the recipient cells through a seeding process (Goedert, 2018; Goedert, Masuda-Suzukake, & Falcon,

2017; Mudher et al., 2017). Inoculation of brain homogenates from human CBD brain extracts into the brains of mice transgenic for wild-type human tau (line ALZ17) recapitulated the hallmark lesions of CBD including astrocytic plaques (Clavaguera et al., 2013). Notably, the same study reported a successful injection of Alzheimer disease (AD), tangle-only dementia, AGD, and PSP human brain homogenates into the hippocampus and overlying cerebral cortex of nontransgenic C57BL/6 mice. A further study described the rapid and distinct cell type-specific spread of pathological tau following intracerebral injections of CBD and AD brain extracts enriched in pathological tau in young human mutant P301S tau transgenic (Tg) mice (line PS19) (Boluda et al., 2015). This supported the concept of *tau strains*; terminology used in prion disease research to describe the phenomenon that disease-associated proteins stably maintain unique conformations that link structure to patterns of pathology. A study using a cell system to isolate tau strains from 29 patients with five different tauopathies, including CBD, found that various diseases are associated with different sets of strains (Sanders et al., 2014). Further supporting this concept, a recent study identified differences in tau strain potency between AD-tau, CBD-tau, and PSP-tau in non-Tg mice, and CBD-tau- and PSP-tau-injected mice showed spatiotemporal transmission of glial tau pathology, suggesting that glial tau transmission contributes to the progression of tauopathies (Narasimhan et al., 2017).

4. Clinical features and clinical criteria

4.1 Clinical presentation: epidemiology, natural history, and prognosis

CBD typically presents in the sixth decade, with a mean age of onset at 63.5 years, ranging from 45 to 77 years (Josephs et al., 2006; Ling et al., 2010a; Wenning et al., 1998). Men and women are equally affected. It is a relentless disease with poor prognosis, having a mean disease duration of 6.6 years, ranging from 2.0 to 12.5 years (Josephs et al., 2006; Ling et al., 2010a; Wenning et al., 1998). This is shorter than PSP and MSA, but CBD patients do not generally die in the first year of illness; otherwise, other causes of rapidly progressive dementia such as CJD should be considered (Josephs et al., 2015). Sepsis and respiratory failure from pneumonia are the most common causes of death (Moscovich et al., 2017; Wenning et al., 1998).

4.2 Clinical manifestation of pathologically confirmed CBD cases

Initially, studies describing the clinical features of pathologically confirmed CBD cases came from clinicopathologic case series, where CBS was the predominant phenotype (Alexander et al., 2014; Grimes, Lang, & Bergeron, 1999; Ikeda et al., 2014; Lee et al., 2011; Murray et al., 2007; Ouchi et al., 2014; Rinne et al., 1994; Wenning et al., 1998). Motor features were the presenting symptoms in the earlier case series, whereas cognitive dysfunction or mixed complaints were the most common initial features in recent series (Murray et al., 2007). CBD patients who do not present with asymmetric parkinsonism at onset are more likely to be misdiagnosed (Litvan et al., 2009). In addition to these motor and cognitive features are other findings, including pyramidal, oculomotor, speech, and psychiatric complaints (Armstrong et al., 2013). Table 1 summarizes the clinical features of pathologically confirmed CBD cases.

4.2.1 Motor features

The most common motor features at presentation are asymmetric limb rigidity, bradykinesia or limb clumsiness, and postural instability (Alexander et al., 2014; Armstrong et al., 2013; Ouchi et al., 2014). As the disease progresses, the proportion of patients having motor symptoms increases to about 76%–85% (Alexander et al., 2014; Armstrong et al., 2013). The

Table 1 Clinical features of pathologically confirmed CBD cases.

Motor features	Higher cortical Dysfunction	Other features
1. **Limb rigidity**	1. **Cognitive impairment (general)**	1. Abnormal eye movements (e.g. apraxia of gaze, vertical supranuclear gaze palsy)
2. **Bradykinesia or clumsy limb**	2. **Behavioral changes**	2. Hyperreflexia and other pyramidal signs
3. **Postural instability**	3. **Limb apraxia**	3. Speech changes
4. Falls	4. Aphasia	
5. Abnormal gait	5. Depression	
6. Axial rigidity	6. Cortical sensory loss	
7. Tremor	7. Alien limb phenomena	
8. Limb dystonia		
9. Myoclonus		

The ones highlighted in bold are the most common motor and cognitive dysfunction features. Adapted from Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., et al. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology, 80*(5), 496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1.

rigidity (Video 1) may be secondary to parkinsonism, dystonia, and paratonia, or a combination of these (Armstrong et al., 2013). Both limb rigidity and bradykinesia are not levodopa responsive; in fact, sustained levodopa responsiveness is considered an exclusion diagnostic criterion for CBD.

Other motor features of CBD include postural instability and falls, gait abnormalities, axial rigidity, tremor, limb dystonia, and myoclonus (Armstrong et al., 2013). The tremor in CBD is often a mixture of resting, postural and action tremors, and sometimes myoclonic jerking erroneously considered as tremors. In CBD and CBS cases, dystonia often affects one arm initially; truncal and leg dystonia were rare (Vanek & Jankovic, 2001). Myoclonus (Video 2) is typically focal, most commonly affecting the upper extremities. It can be spontaneous but is more often stimulus- or action-induced and is considered to be of cortical origin (Ling et al., 2010a; Thompson et al., 1994). In a recent clinicopathologic study, the presence of myoclonus was found more in CBD mimics (e.g., AD) than in actual CBD cases (Alexander et al., 2014).

4.2.2 Cerebral cortical dysfunction

General cognitive impairment, behavioral changes, and limb apraxia are the most common manifestations of cognitive dysfunction in CBD, with a frequency similar to the motor features at the onset, similarly increasing as the disease progresses (Alexander et al., 2014; Armstrong et al., 2013). Aphasia is also seen, but the more commonly alluded cortical sensory loss and alien limb phenomenon are seen less frequently. In a series of pathologically proven CBD, the patients had the most difficulty with learning and word fluency (Vanvoorst et al., 2008). In a similar study, problems with executive functioning and language performance were evident, with relative preservation of memory (Murray et al., 2007). In a recent clinicopathologic study, cognitive impairment in the early stages of CBD was found to be similar to AD dementia and could only be differentiated by the presence of other manifestations, such as motor features (Day et al., 2017). In contrast to AD dementia, patients with CBD had preserved memory early in the disease but had an accelerated worsening of story recall and letter fluency as the disease progressed.

Limb apraxia is common in CBD (Armstrong et al., 2013). Its absence may lead to misdiagnosis, but it is not present in all patients with CBD, despite being considered a core feature in CBD diagnostic criteria (Armstrong et al., 2013; Litvan et al., 1997). Most of the time, it is asymmetric and of the ideomotor type (Video 3), but other types such as limb kinetic

(Video 4), ideational, truncal and orobuccal apraxia also occur (Jacobs et al., 2002; Soliveri, Piacentini, & Girotti, 2005; Zadikoff & Lang, 2005). In the latter stages of the disease, apraxia can be difficult to elicit because of the presence of dystonia, bradykinesia, and rigidity (Boeve et al., 2003). Although commonly mentioned, the alien limb phenomenon (Video 5) is only seen in 30% of CBD cases (Armstrong et al., 2013). This is more than just simple levitation and encompasses several related phenomena including a perception of a limb as foreign and out of voluntary control, involuntary purposeless limb movements, intermanual conflict, enabling synkinesis, grasping, impulsive hand groping, and magnetic apraxia (Armstrong et al., 2013; Boeve et al., 2003; Graff-Radford et al., 2013; Ling et al., 2010a). Cortical sensory loss (e.g. agraphesthesia, astereognosis, loss of two-point discrimination) (Video 6), another key feature, is seen in 25% of cases.

Behavioral changes are also frequent, including a behavioral variant frontotemporal dementia (bvFTD) syndrome. Apathy, antisocial behavior, personality changes, irritability, disinhibition, excessive spending, and hypersexuality are seen at the onset, but as the disease progresses, depression, apathy, and anhedonia are more commonly seen (Armstrong et al., 2013; Ling et al., 2010a; Litvan, Cummings, & Mega, 1998; Murray et al., 2007).

4.2.3 Other clinical manifestations

Abnormal eye movements, signs of pyramidal dysfunction such as hyperreflexia, and speech abnormalities are also described in CBD (Armstrong et al., 2013). However, these features are not common at the onset, and their presence may lead to a diagnosis other than CBD (Litvan et al., 1997). Apraxia of eyelid opening, which is most often a form of pretarsal blepharospasm, is also seen and can cause visual impairment later in the disease course (Ling et al., 2010a). Visuospatial difficulties are occasionally observed, and rarely, these can also be a presenting complaint in CBD (Alexander et al., 2014; Murray et al., 2007; Tang-Wai et al., 2003).

4.3 Clinical syndromes associated with CBD

It is now recognized that the CBD/CBS spectrum is heterogeneous clinically and pathologically. Although CBS is the most common phenotype associated with CBD pathology (37% of cases), CBD can manifest in several clinical phenotypes (Armstrong et al., 2013). Similarly, CBS can be due to several pathologic disorders other than CBD, including PSP, AD, PD, Pick's disease, FTD, and CJD among others (Fig. 2). Although CBD is the most

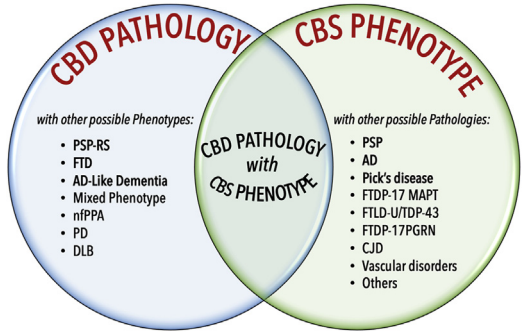

Fig. 2 The spectrum of CBD.CBD pathology is associated with various phenotypes, the most common of which is CBS. Similarly, CBS can be due to various pathologies other than CBD. It is in this context that the complex spectrum of CBD and CBS is simplified and best understood. The ones highlighted in bold are the most common pathologies or phenotypes associated. AD = Alzheimer's disease; CJD = Creutzfeldt–Jakob disease; DLB = Dementia with Lewy Bodies; FTD = Frontotemporal dementia; FTDP = Frontotemporal dementia and parkinsonism linked to chromosome 17; MAPT = Microtubule Associated Protein Tau; nfPPA = non-fluent Primary Progressive Aphasia; PD = Parkinson's disease; PSP-RS = Progressive Supranuclear Palsy-Richardson Syndrome.

common cause of CBS, it accounts for less than 50% of all CBS cases, with PSP and AD being the second and third most common causes (Lee et al., 2011; Ling et al., 2010a; Wadia & Lang, 2007). Five clinical phenotypes account for over 85% of patients in case series: CBS–, PSP–, bvFTD-, non-fluent primary progressive aphasia (nfPPA)-, and an AD-like dementia syndrome; the first four comprise the recently proposed diagnostic criteria for CBS (Tables 2 and 3) (Armstrong et al., 2013). In case series, a noticeable

Table 2 Proposed clinical features associated with the CBS Phenotype.

Syndrome	Motor feature	Higher cortical dysfunction
Probable CBS	*Asymmetric presentation of 2 of*:	*Plus 2 of*:
	1. Limb rigidity or akinesia	**1.** Apraxia (orobuccal or limb)
	2. Limb dystonia	**2.** Cortical sensory deficit
	3. Limb myoclonus	**3.** Alien limb phenomena
Possible CBS	*May be symmetric presentation of 1 of*:	*Plus 1 of*:
	1. Limb rigidity or akinesia	**1.** Apraxia (orobuccal or limb)
	2. Limb dystonia	**2.** Cortical sensory deficit
	3. Limb myoclonus	**3.** Alien limb phenomena

Adapted from Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., et al., … Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology, 80*(5), 496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1.

Table 3 Proposed clinical features associated with other CBD Phenotypes.

Syndrome		Features
Progressive supranuclear palsy syndrome (PSPS)	At least 3 of:	**a.** Axial or symmetric limb rigidity or akinesia **b.** Postural instability or falls **c.** Urinary incontinence **d.** Behavioral changes **e.** Supranuclear vertical gaze palsy or decreased velocity of vertical saccades
Frontal-behavioral-spatial (FBS)	At least 2 of:	**a.** Executive dysfunction **b.** Behavioral or personality changes **c.** Visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia (nfPPA)	Effortful, agrammatic speech plus at least one of:	**a.** Impaired grammar/ sentence comprehension with relatively spared single word comprehension **b.** Groping, distorted speech production (apraxia of speech)

Adapted from Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., et al., … Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology, 80*(5), 496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1.

difference between initial and final clinical diagnoses, attests to the challenge in making a correct diagnosis and the changing phenotype over time.

Of all the different syndromes associated with CBD, it is the CBS phenotype that encompasses most of the clinical manifestations of CBD (Table 2). Although not specific for CBD, CBS is highly suggestive of tau pathology but is also seen with AD and other non-tau pathologies (Josephs et al., 2006). The second most frequently encountered CBD phenotype is the PSP syndrome (Armstrong et al., 2013). Its core features include postural instability, oculomotor dysfunction, and symmetric parkinsonism (Ling et al., 2010a). The presence of more cognitive and behavioral dysfunction and urinary incontinence were found to differentiate patients with CBD from PSP pathology among those with PSP syndrome (Naomi Kouri et al., 2011). The frontal-behavioral-spatial phenotype is a less common syndrome in CBD, with behavioral change, memory impairment and

visuospatial impairments as its characteristic features (Armstrong et al., 2013; Ling et al., 2010a). Extrapyramidal signs and lower motor neuron dysfunction may also occur, and its age at onset is older, in the mid-60s, compared to tau-negative FTLD (Josephs et al., 2006; Rankin et al., 2011). Lastly, CBD may also rarely present with nfPPA in about 5% of cases (Armstrong et al., 2013). Typical of nfPPA are grammatical errors and impaired comprehension (Video 7), and apraxia of speech (Video 8), which is described as a slow, distorted speech (Josephs, et al., 2006). Although an uncommon presentation, the nfPPA has a high correlation with underlying 4R-tauopathy pathology (i.e., either CBD or PSP).

4.4 Clinical diagnostic criteria

Before the 2013 proposed diagnostic criteria, seven previous diagnostic criteria had low sensitivity and specificity, reflecting mostly the CBS phenotype and predicted CBD pathology in only 25%–56% of cases (Armstrong et al., 2013). The new diagnostic criteria were the first to incorporate phenotypes other than CBS. They proposed 2 diagnostic classifications of CBD: (1) "clinical research criteria for probable sporadic CBD" (cr-CBD) and (2) "possible CBD" (p-CBD) (Table 4). The cr-CBD criteria are more restrictive, with higher specificity to minimize the chances of misdiagnosing other pathologies as CBD while the p-CBD criteria are more inclusive, with higher sensitivity, to include clinical presentations associated with CBD pathology other than CBS. In addition, these also include the criteria for the four clinical phenotypes associated with CBD (Tables 2 and 3). Although a common initial clinical diagnosis, the AD phenotype was excluded to avoid a high false-positive diagnosis rate, given the higher prevalence of AD compared to CBD.

Recent attempts to validate the new criteria (Alexander et al., 2014; Boyd et al., 2015; Ouchi et al., 2014; Weinstein et al., 2018) have shown that while the new criteria were found to be more inclusive of the different CBD phenotypes, CBD mimics can still be mistaken as probable or possible CBD cases. Early diagnosis of CBD remains challenging, and about a third of CBD cases do not meet the clinical criteria even late in the disease course. None of the CBD phenotypes had acceptable sensitivity and specificity to predict CBD pathology except for the nfPPA syndrome. One important issue that has impacted these validation studies has been the inclusion of cases of AD; however, the original criteria emphasized the need to use laboratory testing (e.g., CSF or imaging biomarkers) to exclude AD. Since

Table 4 Diagnostic criteria for CBD.

	Clinical research criteria for *probable* sporadic CBD (cr-CBD)	**Clinical criteria for *possible* CBD (p-CBD)**
Presentation	Insidious onset and gradual progression	
Minimum duration of symptoms (years)	1	
Age at onset (years)	≥ 50	1
Family history (>2 relatives)	Exclusion	Permitted
Permitted phenotypes	**(1)** probable CBS, **(2)** FBS or NAV *plus* at least one CBS feature	**(1)** possible CBS, **(2)** FBS or NAV, **(3)** PSPS *plus* at least 1 CBS feature other than limb rigidity or akinesia
Genetic mutation affecting tau (e.g. MAPT)	Exclusion	Permitted
Exclusion criteria for both	**(1)** evidence of Lewy body disease: Classic 4-Hz Parkinson disease resting tremor, excellent and sustained levodopa response, or hallucinations **(2)** evidence of multiple system atrophy: Dysautonomia or prominent cerebellar signs **(3)** evidence of amyotrophic lateral sclerosis: Presence of both upper and lower motor neuron signs **(4)** semantic- or logopenic-variant primary progressive aphasia **(5)** structural lesion suggestive of focal cause **(6)** granulin mutation or reduced plasma progranulin levels; TDP-43 mutations; FUS mutations **(7)** evidence of Alzheimer disease (this will exclude some cases of CBD with coexisting amyloid)	

FBS = frontal-behavioral-spatial; NAV = nonfluent/agrammatic; PSPS = Progressive Supranuclear Palsy Syndrome.
Adapted from Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., et al., … Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology, 80*(5), 496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1.

approximately 50% of false positive cases had AD, the inclusion of these biomarkers would have improved the specificity of the diagnosis; however, sensitivity would likely have remained suboptimal. This is an essential factor to consider when planning future disease-modifying trials in CBD. More sensitive and specific diagnostic criteria will probably require reliable biomarkers (see below).

5. Imaging and other biomarkers

5.1 Neuroimaging findings in corticobasal syndrome

There are numerous neuroimaging modalities that can be used to evaluate patients with CBS/CBD (Table 5). It should be acknowledged from the start that most neuroimaging features associated with the CBS correlate with the location of the pathology, and thus with the clinical manifestations, but not with the specific nature of the pathology.

Table 5 summarizes the findings on structural MRI and other neuroimaging modalities. Structural MRI reveals asymmetric atrophy predominantly involving the posterior frontal and superior parietal lobes, with greater cortical atrophy observed in CBS compared to PSP-RS and MSA-P (Fig. 3) (Grisoli, Fetoni, Savoiardo, Girotti, & Bruzzone, 1995; Koyama, Yagishita, Nakata, Hayashi, Bandoh, & Mizutani, 2007; Soliveri et al., 1999). DTI studies in CBS have demonstrated a variety of abnormalities (Fig. 4), many of which discriminate CBS from both PSP-RS and PD (Rizzo et al., 2008; Whitwell et al., 2014). Change in DTI measures can also be detected over time, with CBS patients showing the most prominent changes in the basal ganglia and widespread supratentorial white matter regions, especially in the pre and postcentral superior parieto-occipital and temporal white matter regions (Zhang et al., 2016). RS-fMRI studies in CBS reflect a higher degree of synchronization in damaged areas and degeneration of association white matter tracts (Bharti et al., 2017). Connectivity from the superior frontal lobe and the thalamus is also found to be abnormal, which may be related to the underlying tau burden but do not show decreased connectivity from the dentate nucleus of the cerebellum as in PSP-RS (Spina et al., 2019; Upadhyay et al., 2017). Reductions in the ratio of NAA/Cr highlight the extent and pattern of severe neuronal damage in these patients (Abe et al., 2000; Tedeschi et al., 1997). Not surprisingly, patterns of hypometabolism on FDG-PET and hypoperfusion on cerebral blood flow SPECT typically mirror the anatomical findings in patients with CBS (Fig. 5). Presynaptic striatal dopamine transporter uptake is typically abnormal in patients with CBS (Fig. 6) but rarely is there reduced uptake with postsynaptic D2 receptors (Hammesfahr et al., 2016; Klaffke et al., 2006; Mille et al., 2017; Pirker et al., 2013; Plotkin et al., 2005). Importantly, involvement of the substantia nigra may not be an early feature in CBD, and a normal presynaptic dopamine imaging does not exclude this diagnosis in the early stages (Ling et al., 2016).

Table 5 Typical neuroimaging findings in CBD and CBS.

Modality	Findings	Clinicopathologic correlate	Differentiation from other disorders	References

Structural MRI	• progressive, asymmetric atrophy affecting the posterior regions of the frontal lobe and the superior parietal lobe
	  • may also affect the white matter adjacent to these cortical regions, middle portion of the corpus callosum, striatum, and thalamus, and temporal lobes,
	  • asymmetric enlargement of the ventricles
	• relatively preserved brainstem anatomy
	• T2 hyperintensity of the globus pallidus
		• atrophy of the premotor and motor cortex, and striatum is associated with the severity of ideomotor apraxia
		• damage to the parietal lobe, premotor cortex and cingulate is associated with the alien limb phenomenon
			• asymmetric frontoparietal atrophy in the context of spared midbrain may help differentiate CBS from PSP-RS.
			• rates of whole brain and basal ganglia atrophy are faster than rates of brain atrophy observed in autopsy-confirmed PSP and AD, reflecting a rapidly progressive disease course
			• in comparison to MSA-P, CBS patients more commonly show global atrophy (100% vs. 36%) and T2 hyperintensity of the globus pallidus.
				Albrecht et al., 2019; Boxer et al., 2006; Dutt et al., 2016; Graff-Radford et al., 2013; Grisoli et al., 1995; Hauser, Murtaugh, Akhter, Gold, & Olanow, 1996; Hess, Christine, Apple, Dillon, & Aminoff, 2014; Huey et al., 2009; Koyama et al., 2007; Sakurai et al., 2015; Schrag et al., 2000; Soliveri et al., 1999; Sudmeyer et al., 2012; Upadhyay et al., 2016.; Whitwell et al., 2007, 2013; Winkelmann, Auer, Lechner, Elbel, & Trenkwalder, 1999; Yamauchi et al., 1998

DTI	• asymmetric degeneration of associative fibers including the	• degeneration of the frontoparietal association fibers may be involved in the	• the asymmetric pattern of white matter tract degeneration provides	Boelmans et al., 2010, 2009; Borroni et al., 2008; Erbetta et al., 2009; Rizzo et al., 2008;

(*Continued*)

Table 5 Typical neuroimaging findings in CBD and CBS.—cont'd

Modality	Findings	Clinicopathologic correlate	Differentiation from other disorders	References
	frontoparietal and intraparietal associative fibers, cingulate bundle, corpus callosum, and corticospinal tract	development of limb apraxia. • degeneration of the corticospinal tracts may explain the occasional pyramidal tract features such as the Babinski sign, hyperreflexia, and spasticity.	an excellent measure for discriminating CBS from both PSP-RS and PD, which typically do not display asymmetry. • compared to PSP-RS, there is greater involvement of supratentorial tracts and less involvement of infratentorial tracts, including the superior cerebellar peduncle. • greater abnormal diffusivity in the corpus callosum is a useful feature in differentiating diagnosis of CBS from PD. • increased ADC values in the putamen appear to be useful in differentiating CBS from PD, but not from PSP-RS.	Tovar-Moll et al., 2014; Upadhyay et al., 2016; Wadia et al., 2013; Whitwell et al., 2014

			• however, the degree of hemispheric asymmetry in ADC could differentiate CBS from PSP-RS	
RS-fMRI	• increased connectivity of affected networks: sensorimotor, executive-control and insula networks • decreased connectivity between the lateral visual and auditory networks • connectivity from the superior frontal lobe and the thalamus is also found to be abnormal.	• connectivity from the superior frontal lobe and the thalamus may be related to the underlying tau burden.	• CBS does not show decreased connectivity from the dentate nucleus of the cerebellum as in PSP-RS	Bharti et al., 2017; Spina et al., 2019; Upadhyay et al., 2017
MRS	• asymmetric ↓ NAA/Cr in the putamen, centrum semiovale, and frontal and parietal lobes • asymmetric ↓NAA/Cho in the striatum and parietal lobe	• MRS findings highlight the extent and pattern of severe neuronal damage.	• as CBS shows more widespread cortical atrophy, reductions in NAA/Cr in the cortex are typically worse than those observed in MSA or PD	Abe et al., 2000; Tedeschi et al., 1997

(*Continued*)

Table 5 Typical neuroimaging findings in CBD and CBS.—cont'd

Modality	Findings	Clinicopathologic correlate	Differentiation from other disorders	References
FDG-PET and cerebral blood flow SPECT	• asymmetric hypometabolism and hypoperfusion in the lateral premotor cortex, supplementary motor area, motor cortex, prefrontal lobes, superior parietal lobes, striatum and thalamus	• these findings typically mirror the anatomical findings in structural MRI, as well as location of pathological findings, but do not predict the nature of underlying tau pathology.	• compared to PSP-RS, FDG-PET and SPECT abnormalities are usually more severe and widespread, with greater involvement of the parietal lobes and less involvement of the midbrain. • automated machine learning type techniques applied to FDG-PET also differentiate CBS from other parkinsonian disorders	Brajkovic et al., 2017; Garraux et al., 2013; Hellwig et al., 2012; Hosaka et al., 2002; Huang, Lu, Kao, & Tsai, 2007; Juh, Pae, Kim, Lee, Choe, & Suh, 2005; Koyama et al., 2007; Laureys et al., 1999; Mille et al., 2017; Niethammer et al., 2014; Tripathi et al., 2013; Turaga, Mridula, & Borgohain, 2013; Zalewski, Botha, Whitwell, Lowe, Dickson, & Josephs, 2014; Zhao, Zhang, & Gao, 2012
Dopaminergic imaging	• asymmetric decreased presynaptic binding in the caudate and putamen • rarely show reduced postsynaptic binding	• involvement of the substantia nigra may not be an early feature in CBD; a normal presynaptic dopamine imaging does not exclude this diagnosis in the early stages.	• uptake is typically greater than that observed in PD • in contrast to PSP-RS, CBS patients rarely show reduced uptake with postsynaptic D2 receptors.	Cilia et al., 2011; Hammesfahr et al., 2016; Klaffke et al., 2006; Laureys et al., 1999;Ling et al., 2016; Mille et al., 2017; Pirker et al., 2013; Plotkin et al., 2005

Tau-PET imaging, using [^{18}F] Flortaucipir, [^{18}F] THK-5351, [^{11}C]PBB3	• asymmetric increased tau uptake in the precentral and postcentral cortex, superior frontal and parietal lobe, putamen, globus pallidus
	  • the degree of uptake is variable, with some patients showing no evidence for elevated tau uptake.
	  • ligand uptake was observed in both the gray matter and the adjacent white matter.
		• uptake is usually asymmetric, with greatest involvement in the hemisphere contralateral to the affected limb.
		• there is some evidence that the degree of uptake may be related to disease severity, and the clinical presentation.
		• uptake is not truly reflective of tau burden in 4R tauopathies but some studies have shown that the degree of regional tau-PET uptake across the brain correlated well with the regional distribution of tau pathology.
			• the interpretation of tau-PET findings in CBS is problematic because the underlying pathology in CBS is heterogeneous and hence it is unclear whether the reported CBS cases actually had CBD.	Ali et al., 2018; Cho et al., 2017; Josephs et al., 2016; Kikuchi et al., 2016; Lowe et al., 2016; Marquie et al., 2015; Maruyama et al., 2013; McMillan et al., 2016a,b; Niccolini et al., 2018; Sander et al., 2016; Smith et al., 2017; Tsai et al., 2019

AD = Alzheimer's disease, ADC = Apparent Diffusion Coefficient, CBD=Corticobasal Degeneration, CBS=Corticobasal Syndrome, DTI = diffusion-weighted and diffusion tensor imaging, FDG-PET = [^{18}F]fluorodeoxyglucose PET, MRI = magnetic resonance imaging MRS = magnetic resonance spectroscopy (MRS), MSA = Multiple System Atrophy, MSA-P = Multiple System Atrophy-Parkinsonian Type, NAA/Cr=N-acetylaspartate/Creatine, NAA/Cho = N-acetylaspartate/Choline, PD=Parkinson's Disease, PET = positron emission tomography (PET), RS-fMRI = resting-state functional MRI (RS-fMRI), SPECT = single-photon emission computerized tomography (SPECT) imaging.

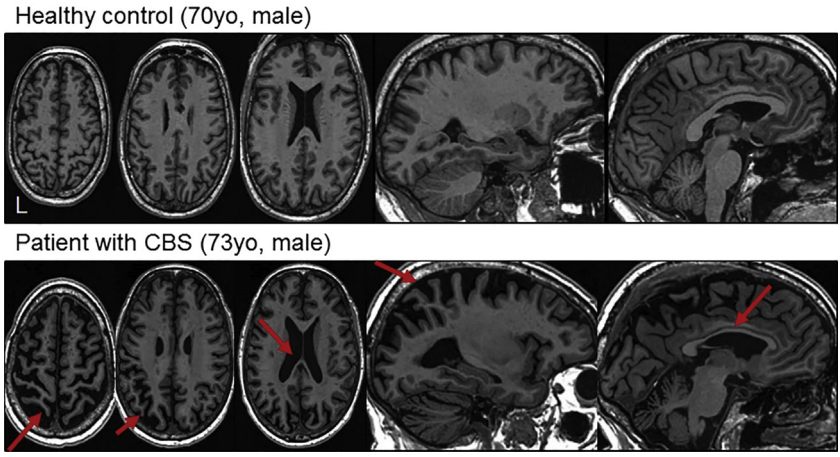

Fig. 3 ***Structural MRI in a healthy control and patient with CBS.*** The CBS patient displays atrophy of premotor and motor cortex, parietal lobes and body of the corpus callosum, and expansion of the lateral ventricles, particularly in the left hemisphere.

Autopsy studies have shown that neuroimaging features observed in CBS can vary somewhat according to the underlying pathology. All patients, regardless of pathology, show core features on neuroimaging, including atrophy in the premotor cortex (Whitwell et al., 2010). Greater additional involvement of the temporal and parietal lobes is suggestive of underlying AD pathology while greater involvement of the prefrontal cortex is predictive of FTLD, and involvement of the midbrain is suggestive of underlying PSP (Fig. 7) (Hu et al., 2009; Josephs et al., 2010; Lee et al., 2011; McMillan, Boyd, et al., 2016; Pardini et al., 2019; Whitwell et al., 2010). Generally, more widespread patterns of atrophy point toward an underlying AD or FTLD, whereas more focal patterns predominantly involving the premotor cortex suggest an underlying tauopathy (CBD or PSP) (Whitwell et al., 2010). There is also a suggestion that the efficiency of fronto-temporo-parietal structural networks measured using DTI differs according to the pathology in CBS, and can also predict the presence of AD pathology (based on autopsy and CSF biomarkers) (Medaglia et al., 2017).

The availability of molecular PET ligands that can bind to beta-amyloid has also provided an in vivo biomarker for the presence of AD-type pathology. Approximately 28–44% of CBS patients show beta-amyloid deposition on PET scanning (Burrell, Hornberger, Villemagne, Rowe, & Hodges, 2013; McMillan, Boyd, et al., 2016; Sha et al., 2015). CBS patients

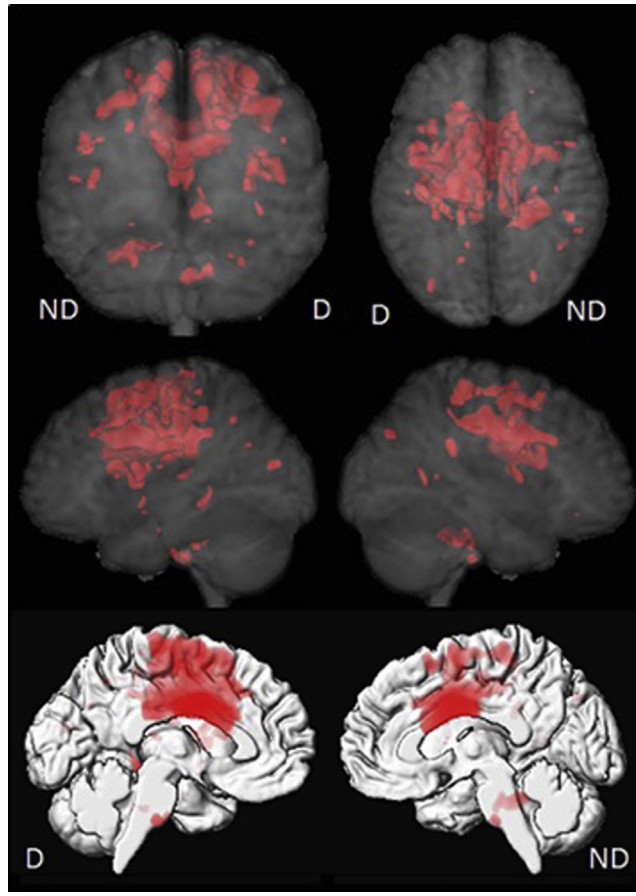

Fig. 4 ***Diffusion tensor imaging abnormalities in CBS compared to controls.*** Reduced diffusivity (measured using fractional anisotropy) is observed throughout the white matter underling the premotor and motor cortex, and in the body of the corpus callosum, with greater abnormalities observed in the dominant hemisphere.

that are amyloid (+) on PET tend to show greater atrophy in the posterior temporal lobe compared to amyloid (-) patients (Burrell et al., 2013).

The degree of uptake using currently available tau ligands such as [^{18}F] flortaucipir, [^{18}F]THK-5351 and [^{11}C]PBB3 in CBS is variable, with some patients showing no evidence for elevated tau uptake (Fig. 8) (Ali et al., 2018; Maruyama et al., 2013; Tsai et al., 2019). The interpretation of tau-PET findings is difficult for two main reasons. The first is that the underlying pathology in CBS is heterogeneous and hence it is unclear whether the reported CBS cases actually had CBD, and hence 4R tau pathology.

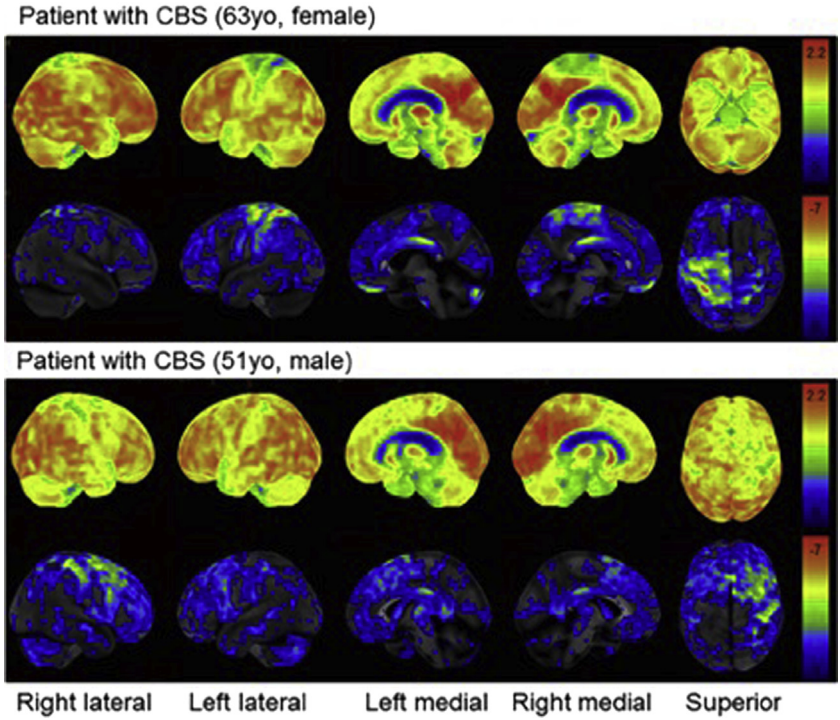

Fig. 5 ***FDG-PET scans from two patients with CBS.*** Top row shows color-coded standard uptake value ratio images normalized to the pons, while bottom row shows an age-corrected Z-score map of hypometabolism compared to a control cohort generated using CortexID software. Both patients show asymmetric hypometabolism predominantly in the posterior frontal and superior parietal lobes and corpus callosum/cingulate gyrus, with milder regions of hypometabolism observed in the prefrontal cortex and temporal lobes.

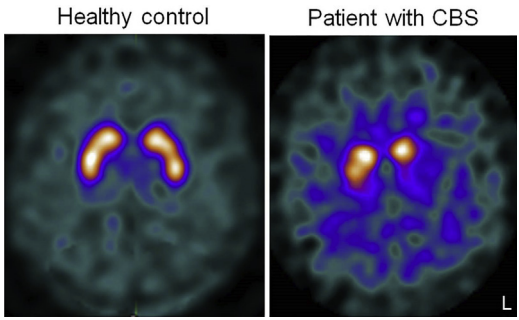

Fig. 6 ***DAT scan SPECT scans from a healthy control and a patient with CBS.*** The patient with CBS shows decreased DAT uptake bilaterally within the putamen, worse on the left, with normal caudate nuclei.

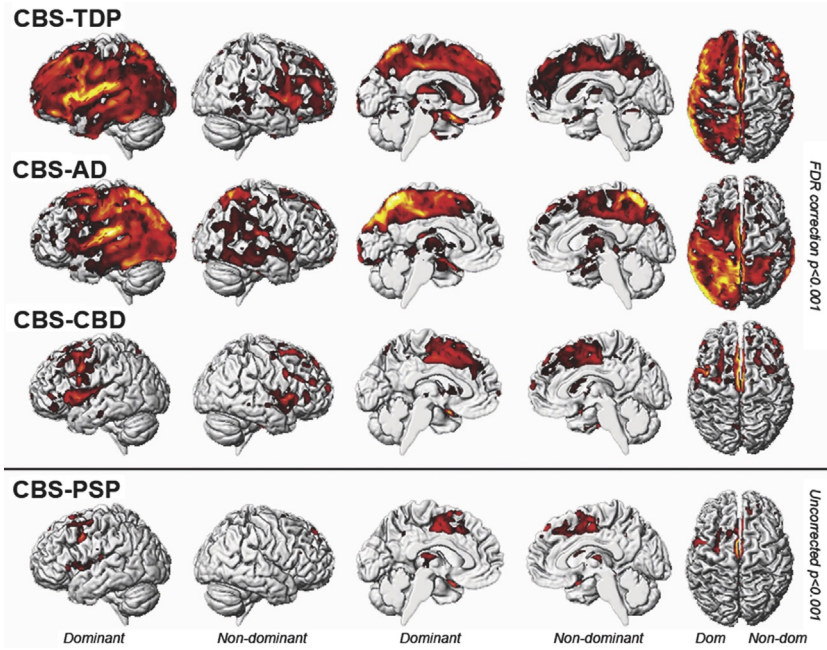

Fig. 7 Three-dimensional renderings show patterns of gray matter atrophy in patients with CBS with different underlying pathologies. Surface renderings showing regions of gray matter loss in the dominant and nondominant hemisphere of CBS-TDP, CBS-AD, CBS-CBD, and CBS-PSP compared to controls. All results are shown after correction for multiple comparisons using the false discovery rate (FDR) at $p < 0.001$, except for the results from the CBS-PSP group, which are shown uncorrected at $p < 0.001$. *Figure reproduced with permission from Whitwell, J. L., Jack Jr, C. R., Boeve, B. F., Parisi, J. E., Ahlskog, J. E., Drubach, D. A., et al. (2010). Imaging correlates of pathology in corticobasal syndrome.* Neurology, *75(21), 1879–1887. https://doi.org/10.1212/WNL.0b013e3181feb2e8. AD = Alzheimer disease; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; TDP = TDP-43 immunoreactivity.*

Second, autoradiographic studies have shown little to no binding of these ligands to 4R tau in the brain. The currently available tau-PET ligands were developed for AD and show strong binding to the 3R+4R tau found in this disease. Thus, uptake may not truly reflect tau burden in 4R tauopathies (Lowe et al., 2016; Marquie et al., 2015; Sander et al., 2016). Indeed, tau PET studies have found that the degree of flortaucipir and THK-5351 uptake can be greater in amyloid (+) CBS patients, with the degree of uptake in a similar range to that observed in AD, suggesting these patients have

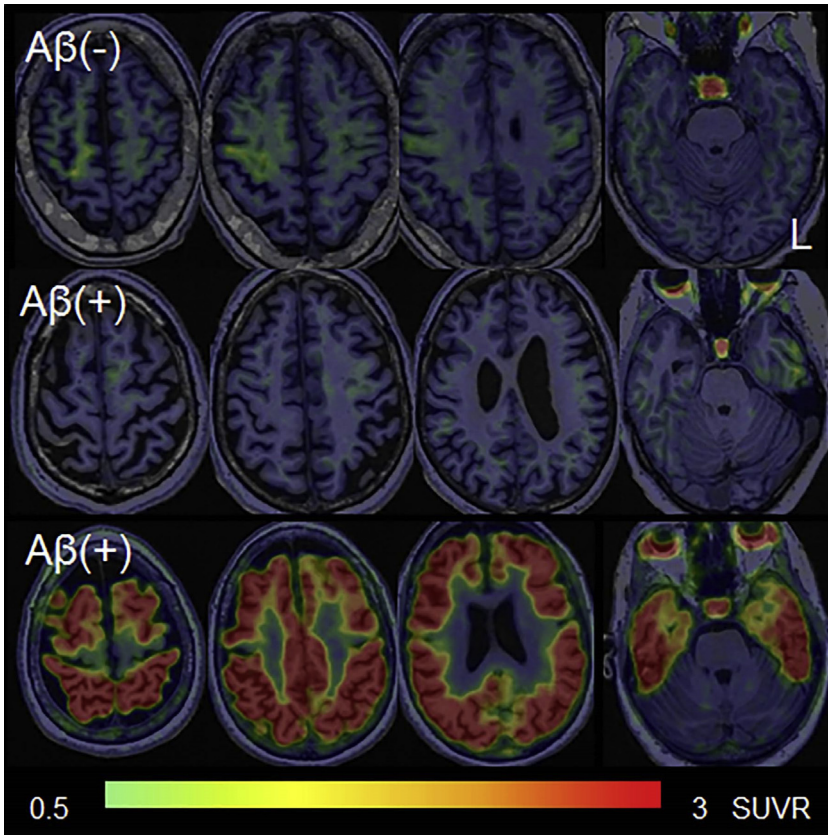

Fig. 8 ***[^{18}F]flortaucipir PET scans in three patients with CBS.*** The patient in the top row is beta-amyloid negative on PET scanning and shows elevated flortaucipir uptake in premotor and motor cortex, with greater uptake in the right hemisphere. The patient in the middle row has beta-amyloid deposition on PET scanning but shows very little uptake on flortaucipir PET. The patient in the bottom row has beta-amyloid deposition on PET scanning and shows striking elevated uptake on flortaucipir PET throughout the cortex.

an underlying AD pathology (Fig. 8) (Ali et al., 2018; Kikuchi et al., 2016; Smith et al., 2017; Tsai et al., 2019; Xia et al., 2017). However, amyloid (+) CBS cases do not always show high levels of uptake on tau PET (Fig. 8) (Kikuchi et al., 2016; Tsai et al., 2019). Furthermore, two studies have shown that the degree of regional tau-PET uptake across the brain correlated well with the regional distribution of tau pathology at autopsy in two CBD patients (Josephs et al., 2016; McMillan, Irwin, et al., 2016). However, it is still possible that the ligands are only binding a small fraction

of the total 4R-tau burden or are binding to other targets. More selective tau PET ligands developed specifically for 4R tauopathies are clearly needed to advance the field.

5.2 Neuroimaging findings across other clinical presentations of CBD

Not surprisingly, the neuroanatomic features of the other phenotypes associated with CBD differ somewhat from those presenting with CBS (Josephs et al., 2008). CBD patients who present with nfPPA tend to show a focus of atrophy and hypometabolism in posterior regions of the frontal lobe, including the inferior, middle and superior frontal gyri and premotor cortex, as well as the striatum and insula (Fig. 9) (Josephs et al., 2006; Lee et al., 2011; Santos-Santos et al., 2016; Tetzloff et al., 2018). The motor cortex and parietal lobe can become involved later in the disease course coinciding with the development of clinical features of CBS (Tetzloff et al., 2018). In addition, these patients may show elevated uptake on flortaucipir tau PET in the putamen, pallidum, thalamus, precentral cortex, rolandic operculum, supplemental motor area, and left Broca's area (Josephs et al., 2016). Most studies have reported left-sided patterns of neurodegeneration, but right-sided patterns of neurodegeneration have also been observed in patients with apraxia of speech (Assal, Laganaro, Remund, & Ragno Paquier, 2012; Josephs et al., 2006; Lee et al., 2011; Santos-Santos et al., 2016; Spinelli et al., 2015; Tetzloff et al., 2018).

Patients with CBD-bvFTD show atrophy of the posterior lateral and medial frontal lobe, including the supplementary motor area, and striatum, and also the orbitofrontal, dorsomedial and dorsolateral prefrontal cortex (Fig. 10) (Lee et al., 2011; Whitwell et al., 2011). Both asymmetric and symmetric patterns have been observed (Hassan et al., 2010; Lee et al., 2011).

An autopsy-confirmed CBD patient with a PSP phenotype showed atrophy in typical CBD-related regions, including the frontal and parietal lobes and basal ganglia, and also showed atrophy of midbrain, consistent with its phenotype (Whitwell et al., 2013). Elevated flortaucipir uptake on PET was also observed in the substantia nigra, globus pallidus, midbrain and frontal lobe, similar to patterns observed in PSP-RS (Cho et al., 2017; Whitwell et al., 2017). CBD patients that present with posterior cortical atrophy tend to show symmetric patterns of atrophy and hypometabolism primarily on the occipital lobe, also spreading to parietal and temporal regions, with patterns typical for PCA(Fig. 10) (Jellinger et al., 2011; Lee et al., 2011; Whitwell et al., 2007).

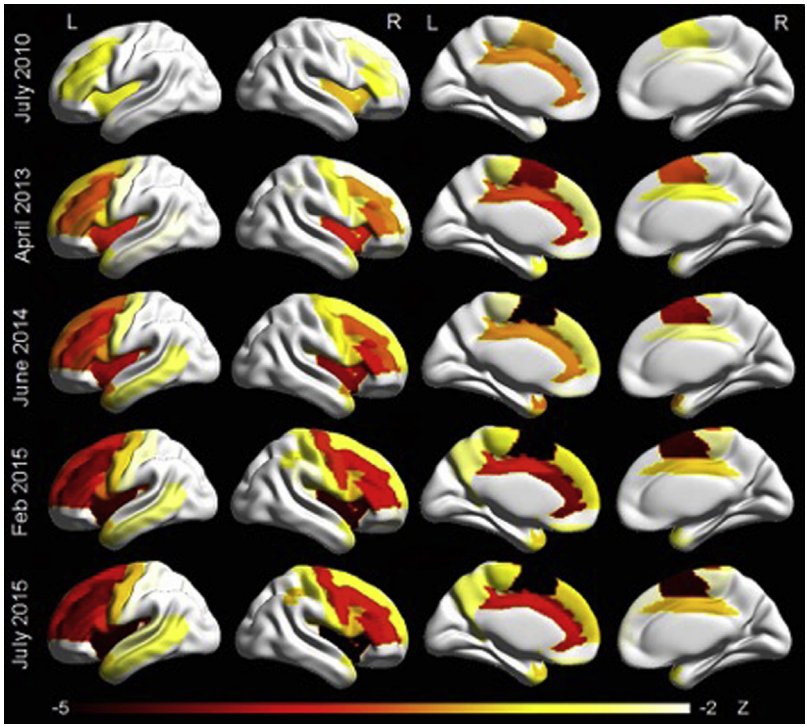

Fig. 9 ***Three-dimensional renders showing progression of regional atrophy on MRI in a patient with progressive apraxia of speech that had autopsy confirmed CBD.*** Each region in the automated anatomical labeling atlas has been assigned a Z score representing atrophy compared to matched controls. Renders were created using BrainNet viewer. At the first MRI approximately five years from onset, the patient shows atrophy of the supplementary motor area, anterior cingulate, middle cingulate and right insula, with less severe involvement of the middle frontal gyrus, frontal inferior triangularis and opercularis, left superior frontal gyrus, left paracentral lobule, and right caudate and putamen. These regions remain the most severely affected over time, although atrophy spreads to involve the motor cortex, temporal lobe, and parietal lobe over time. *Figure is reproduced with permission from Tetzloff, K. A., Duffy, J. R., Strand, E. A., Machulda, M. M., Boland, S. M., Utianski, R. L., et al. (2018). Clinical and imaging progression over 10 years in a patient with primary progressive apraxia of speech and autopsy-confirmed corticobasal degeneration.* Neurocase, 24*(2), 111—120. https://doi.org/10.1080/13554794.2018.1477963*.

5.3 CSF biomarkers in corticobasal syndrome

Cerebrospinal fluid (CSF) biomarkers also have the potential for diagnostic utility in CBS. CSF concentrations of the neurofilament light chain (NfL), which acts as a surrogate marker of neurodegeneration, are elevated in CBS patients compared to controls and AD (Alcolea et al., 2017; Hall et al., 2012;

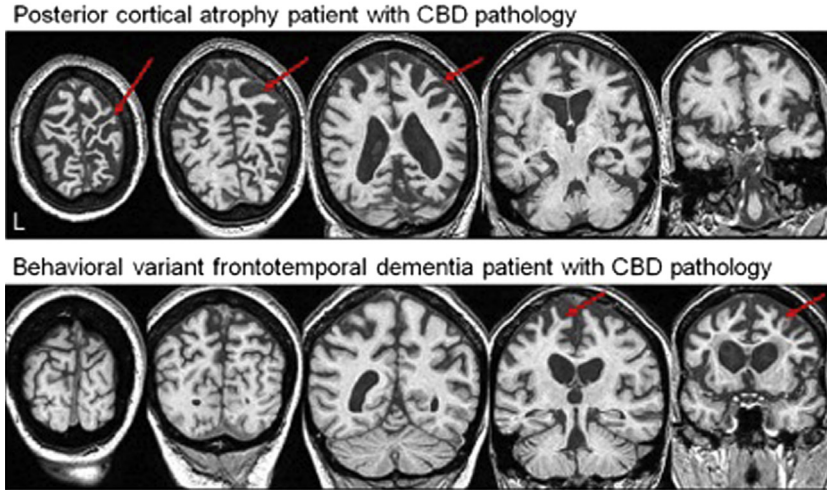

Fig. 10 ***Structural MRI from two patients that had autopsy confirmed CBD with different clinical presentations.*** The posterior cortical atrophy patient shows striking atrophy of the occipital and parietal lobes, while the behavioral variant of frontotemporal dementia patient shows atrophy of the posterior frontal lobe and prefrontal cortex.

Olsson et al., 2018; Scherling et al., 2014). Elevated CSF NfL is also observed in PSP-RS and MSA, but not in PD, and, thus, can differentiate CBS from PD but not from other atypical parkinsonian disorders (Hall et al., 2012; Olsson et al., 2018; Scherling et al., 2014). In addition, lower levels of soluble α and β fragments of amyloid precursor protein (sAPP), and higher levels of YKL-40, a marker of inflammation, also differentiate CBS from PD (Alcolea et al., 2017; Magdalinou et al., 2015). Combining nine CSF biomarkers, including NfL, sAPP, and YKL-40 can differentiate CBS from PD with high accuracy (Magdalinou et al., 2015). However, while sAPPβ is lower in CBS compared to AD, the levels in CBS do not differ from those seen in PSP and FTD (Alcolea et al., 2017). Similarly, YKL-40 is typically also elevated in PSP-RS, AD, and FTD (Alcolea et al., 2017). Other CSF biomarkers have been investigated, including FGF-5, FGF-19, and SPOCK1, but the diagnostic accuracy of NfL is still superior in distinguishing atypical parkinsonsm from PD (Jabbari et al., 2019). Some biomarkers, such as NfL, may also be used as prognostic or as monitors of disease progression, independent of underlying pathologies.

The classic CSF biomarkers for AD, including Aβ42, t-tau, and p-tau, are useful in differentiating CBS-AD from cases of CBS-CBD (Magdalinou et al., 2015; Scherling et al., 2014). However, these biomarkers are

unhelpful in differentiating between parkinsonian disorders, which would be important in selecting patients for future disease-specific trials (e.g., disease-modifying therapies). It may be less important to distinguish CBD from PSP in this regard if treatments targeting tau can influence disease progression in both of these 4R tauopathies.

6. Current treatments

6.1 Disease-modifying treatment

At present, there is no effective disease-modifying therapy for CBD. It is hoped that advances in the understanding of disease pathogenesis and the discovery of effective disease-modifying therapies in other tauopathies, particularly PSP, will have an impact on CBD. Previous studies have shown that mitochondrial dysfunction has a role in tauopathies. Thus, coenzyme Q10 (CoQ10) was hypothesized to restore normal mitochondrial function; however, a randomized trial of CoQ10 in PSP failed to provide benefit (Stamelou et al., 2008). Another potential target for neuroprotection in CBD is the inhibition of glycogensynthase kinase 3 (GSK-3). By inhibiting GSK-3, lithium could potentially block tau phosphorylation, but an open-label trial in PSP (clinicalTrial.gov identifier NCT00703677) was terminated due to poor tolerability (Moretti, 2019). Another GSK-3 inhibitor, tideglusib, failed to show benefit in a phase 2 trial in PSP (Tolosa et al., 2014). A large phase 2-3 study of riluzole in PSP and MSA failed to demonstrate disease modifying effects (Bensimon et al., 2009). Davunetide, a drug that promotes microtubule stabilization, was investigated in a 52-week randomized, double-blind, placebo-controlled trial in PSP but was not shown to be effective (Adam L Boxer et al., 2014). There is an ongoing RCT on TPI 287 (clinicalTrial.gov identifier NCT0213384) among patients with primary 4R-tauopathies. This is a taxane which is also aimed at promoting microtubule stabilization, but it has recently been reported to be poorly tolerated and has not shown significant benefits to date (Medina, 2018; Moretti, 2019). Encouraged by the concept of cell-to-cell tau propagation (Jadhav et al., 2019), another possible disease-modifying therapy using monoclonal antibodies against tau is actively being investigated in phase 2 trials in PSP (Jadhav et al., 2019) and a phase 1 study involving patients with CBS (clinicalTrial.gov identifier NCT03658135). Unfortunately, the first trial in PSP-RS has been terminated due to futility (clinicalTrial.gov identifier

NCT02985879). Several other approaches, both directed at a toxic gain of function and a loss of the normal microtubular binding function of tau may be pursued in the future (Boxer et al., 2017).

6.2 Symptomatic treatment

6.2.1 Parkinsonism

Several retrospective studies in CBS and CBD have shown that levodopa provides a transient and minimal improvement of parkinsonism (Boeve et al., 1999; Kompoliti et al., 1998; Ling et al., 2010a). Nonetheless, patients with clear parkinsonism could still be given a trial of levodopa 800–1500 mg per day up for at least two months before gradually decreasing the dose if the patient does not experience clinical improvement (Lamb, Rohrer, Lees, & Morris, 2016; Marsili, Suppa, Berardelli, & Colosimo, 2016). Levodopa should not be discontinued abruptly as sometimes, patients may notice an unrecognized modest benefit as the dose is reduced (Armstrong, 2014). Complications of therapy, such as levodopa-induced dystonia and choreiform movements occur in about 17% of cases (Ling et al., 2010a), while 5% of patients report worsening of parkinsonism, dystonia, myoclonus, and gait dysfunction (Kompoliti et al., 1998).

Amantadine has also been tried in CBS at doses of 300–600 mg per day, but the evidence from case reports and case series show little if any clinical improvement (Colosimo, Merello, & Pontieri, 1996; Mahapatra, Edwards, Schott, & Bhatia, 2004). In a retrospective study, amantadine improved rigidity, tremor, and gait in 3/24 patients (Kompoliti et al., 1998). There were also other medications reported in that study, including dopamine agonists (bromocriptine and pergolide), selegiline, and anticholinergics, but overall, only 24% reported clinical improvement but again this was an uncontrolled retrospective chart review with no pathology correlation.

6.2.2 Myoclonus

Myoclonus can be symptomatically treated with the usual medications used for myoclonus. Benzodiazepines, particularly clonazepam, was said to improve myoclonus in 23% of patients (Kompoliti et al., 1998). Levetiracetam has also been reported to be effective in controlling myoclonus (Cho & Lee, 2014; Kovács et al., 2009). **Valproic acid, piracetam, and gabapentin** may also be considered (Moretti, Binetti, Zanetti, & Frisoni, 2014). Despite these reports, myoclonus is often very resistant to pharmacotherapy.

6.2.3 Limb dystonia

Overall, levodopa does not provide any benefit for dystonia in CBS. In a retrospective review, small numbers of cases have been reported to respond to benzodiazepines, baclofen, and anticholinergics (Kompoliti et al., 1998). Chemodenervation with botulinum toxin is the best option for dystonia, with an improvement in pain, abnormal posture and ease for maintaining hygiene (Kompoliti et al., 1998; Mahapatra et al., 2004; Müller, Wenning, Wissel, Seppi, & Poewe, 2002; Shehata, Shalaby, Esmail, & Fahmy, 2015; Vanek & Jankovic, 2001). Patients with dystonic clenched fists should be assessed for wounds and secondary infection.

6.2.4 Eyelid opening apraxia and dry eyes

Eyelid opening apraxia is best addressed by pretarsal orbicularis occuli botulinum toxin injections (Lang, 2005). Acetylcysteine, carbomers, and 0.9% sodium chloride ophthalmic drops, and artificial tears are useful in the treatment of dry eyes due to eyelid dysmotility (Lamb et al., 2016).

6.2.5 Non-motor symptoms

There is no evidence regarding the beneficial effect of acetylcholinesterase inhibitors (AChEIs) and memantine for dementia in CBD. Off-label use of these medications in CBD is based only on anecdotal experience (Lamb et al., 2016). It is possible that patients who obtain some improvement are those with underlying AD or even PD dementia (Armstrong, 2014; Marsili et al., 2016). However, clinicians must be aware of the potential worsening of symptoms when prescribing these medications. An open-label trial on rivastigmine in FTD showed improvement in behavior and caregiver burden, but a study of donepezil in bvFTD and PPA showed a deterioration of behavior, with increased disinhibition and compulsive behavior (Mendez, Shapira, McMurtray, & Licht, 2007; Moretti et al., 2004). Another study showed that when donepezil was discontinued, there was an improvement in the patients' behavioral symptoms and caregiver burden (Kimura & Takamatsu, 2013). Thus, risks versus benefits must be weighed carefully.

With the debilitating nature of their disorder, CBD patients often have depression. There are currently no randomized controlled trials of antidepressants in CBD. SSRIs, such as sertraline and citalopram, and cognitive behavioral therapy may be tried to address depression, anxiety, and obsessive-compulsive features in CBD (Armstrong, 2014). Tricyclic antidepressants (TCAs), such as amitriptyline, can also be used to treat depressive

symptoms (Lamb et al., 2016). With its anticholinergic properties, TCAs may also help improve sialorrhea but could worsen cognitive dysfunction. Atypical antipsychotics, preferably clozapine and quetiapine, as well as mood-stabilizing agents, e.g., carbamazepine and valproic acid, can be used for agitation and aggression, but caution must be taken as these drugs can worsen parkinsonism and cognitive dysfunction (Marsili et al., 2016).

Sialorrhea could be treated with small doses of anticholinergics, such as glycopyrrolate and atropine drops (Lamb et al., 2016). Botulinum toxin injection is also an effective and safe form of treatment (Gómez-Caravaca et al., 2015). Dysphagia should be adequately evaluated by a speech and language pathologist, especially since aspiration is a common cause of death in CBD. Diet modifications, use of thickeners, swallowing maneuvers may be tried in those with mild to moderate dysphagia. When dysphagia becomes severe, feeding tubes and gastrostomy may be considered to prevent aspiration and to ensure adequate nutrition. Constipation can usually be easily addressed by increasing fluid and dietary fiber intake and with the use of laxatives.

6.3 Surgical treatment

As with most atypical parkinsonism disorders, patients with CBD do not benefit from deep brain stimulation since symptoms that do not respond to levodopa fail to respond to DBS. There is only one reported case of CBD who underwent DBS for tremors mistaken as essential tremors, with the patient having suboptimal results (Okun et al., 2005).

6.4 Non-pharmacologic treatment and palliative care

Early in the disease, supportive management should be initiated. This includes physical and occupational therapy, as well as falls prevention programs to maintain mobility and thereby preserve some degree of functional independence. Apraxia is an important source of disability that compromises the potential benefit from the usual physiotherapy approaches. Speech therapy should also be advised to improve communication and swallowing difficulties and to prevent aspiration. Guidance from dieticians may be needed to ensure adequate nutrition. As the disease progresses, significant disability and caregiver burden become inevitable. Social workers may be needed eventually, and the focus of supportive management is shifted toward safety and comfort rather than physical independence. The use of wheelchairs, railings, commodes, and hospital beds at home should be discussed with the patient and the family. Caregiver fatigue/burnout should also be evaluated at

every clinic visit. When acceptable to the patient and their family, medical assistance in dying (MAID) can also be offered to in selected countries.

7. Unmet needs and future treatments

Research studies are needed to improve the accuracy of the diagnosis of CBD, especially in the identification of cases in the early stages of the disease. More work is required to understand the biological underpinnings of the currently available tau PET ligands and, ideally, new ligands are needed that perform better in the context of 4R tauopathies. Furthermore, a more meticulous and detailed clinical phenotyping of possible CBD patients is essential in revising the diagnostic criteria. Sensitive and specific diagnostic criteria are particularly important when enrolling patients in research studies and clinical trials. Until reliable biomarkers and disease-specific treatments are available, lumping the different clinical phenotypes associated with CBD with those associated with PSP, while excluding those with a clear non-4R tauopathy pathology, should be considered to include as many patients as possible in research studies of 4R tauopathies. Further molecular studies on tau pathology in CBD will continue to shed light not only on the pathophysiologic mechanisms underlying the neurodegeneration associated with abnormal tau accumulation but will also contribute to the development of new treatment options. At present, therapeutic options for CBD remain symptomatic, with disease-modifying therapies being unavailable. Clinical trials of monoclonal antibodies against tau are actively being pursued in PSP. It is expected that this and other anti-tau therapeutic strategies will also be applied in CBD, in the hope of slowing the progression of this relentless disease. Since these trials need to employ clinical rating scales, neuroimaging, and biochemical markers to evaluate disease progression or clinical improvement. New methods of evaluating outcomes of this clinically heterogenous disease are required. For example, a patient/caregiver reported functional scale (the Cortical Basal Ganglia Functional Scale, CBFS) is currently under development.

Supplementary materials

Supplementary data related to this article can be found online at https://doi.org/10.1016/bs.irn.2019.10.014.

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