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The corticobasal syndrome–Alzheimer’s disease conundrum

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Abstract

Corticobasal syndrome (CBS), once thought to be pathognomonic for corticobasal degeneration pathology, is increasingly reported with various underlying pathologies. Alzheimer’s disease is one such pathology, also once believed to be unique for its clinical syndrome of dementia of the Alzheimer’s type. CBS is believed to result from topography of asymmetric parietofrontal cortical lesion involvement, rather than lesion subtype. However, this topographical pattern is strikingly different to that typically associated with AD for unclear reasons. This article will focus on CBS with underlying AD pathology (CBS-AD), and will review associated clinical, imaging and demographic factors. Predicting AD pathology is of marked interest as disease-modifying therapies loom on the horizon, with biomarkers and imaging research underway. By reviewing the literature for CBS-AD case reports and series and contrasting them with CBS with underlying corticobasal degeneration pathology cases, the article aims to examine factors that may predict AD pathology. How AD pathology may produce this clinical phenotype, rather than the prototype dementia of the Alzheimer’s type, will also be reviewed.

Keywords

alien limb; Alzheimer’s disease; apraxia; corticobasal degeneration; corticobasal syndrome; dementia; myoclonus; rigidity; tau; voxel-based morphometry

Corticobasal syndrome (CBS) is a striking and unusual clinical manifestation of various neurodegenerative pathologies, with tauopathies being the most common. The prototype pathology is corticobasal degeneration (CBD), estimated to account for 50% of cases [1]. Other pathologies reported in the literature include Alzheimer’s disease (AD) [2,3], progressive supranuclear palsy (PSP) [4], frontotemporal dementia with parkinsonism linked to chromosome 17, Pick’s disease with Pick bodies, dementia with Lewy bodies [1,5], neurofilament inclusion body disease [6], Creutzfeldt-Jakob disease [7], frontotemporal degeneration due to progranulin gene mutation [8] and motor neuron inclusion body dementia [9]. Unifying the pathologies that produce CBS is a consistent topographic distribution of cortical damage, involving frontal or frontoparietal cortex in an asymmetric fashion [7].

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The focus of this article will be on CBS resulting from underlying AD pathology, hereafter termed CBS-AD. This association is of particular interest as CBD and AD are distinct neurodegenerative pathologies and share relatively little in common apart from abnormal phosphorylated tau protein deposition. Features that set AD apart from CBD include the specific tau protein isoform deposited, the presence of β -amyloid deposition, the clinical hallmark of dementia of the Alzheimer's type (DAT), and the presence of medial temporal lobe atrophy. To state this latter point further, the brain regions implicated to clinically produce CBS are typically different from those involved in typical AD pathology, hence the conundrum. Ironically, CBD and AD pathology were thought to be pathognomonic for their clinical syndrome, CBS and DAT, respectively. Clinicopathological overlap amongst the tauopathies is now increasingly appreciated, including CBS with AD pathology and dementia with CBD pathology [10]. This article will explore reasons why the topography of AD pathology may vary to produce this distinct syndrome. Factors that may predict underlying AD pathology in cases presenting with CBS will also be examined. Many clinicians have called for further research to look at clinical markers of AD pathology in CBS [3,11,12]. Trying to accurately predict pathology is of great importance, as therapies are typically specific to the underlying disease process. For example, AD may benefit from cholinesterase inhibitors or future AD-modifying therapies that may be ineffective in CBD.

Corticobasal syndrome

This rare clinical syndrome is associated with sporadic disease with typical onset in the sixth to eighth decades. Core clinical features are insidious progressive asymmetric rigidity and apraxia, accompanied by symptoms and signs of cortical (motor, sensory or association cortices) and extrapyramidal dysfunction [13]. Cortical signs include cortical sensory loss, alien limb phenomena, myoclonus, apraxia, pyramidal motor signs, agrammatic aphasia, apraxia of speech and visuospatial impairment. Extrapyramidal involvement includes dystonia and levodopa nonresponsive Parkinsonism (rigidity, tremor and bradykinesia). Typical mean survival is 7 years from symptom onset. Asymmetry is emphasized, although symmetric presentations have been described [14]. Thus clinical findings may be explained by the topographical distribution of cortical damage: cortical sensory loss and apraxia occur with parietal lesions, and occasionally posterior frontal lesions; frontal or parietal lesions can produce alien limb syndrome [15], mirror movements [16], pyramidal tract signs or apraxia; and posterior inferior frontal lesions can produce agrammatic aphasia [17]. The lack of a marked response to levodopa is postulated to reflect postsynaptic nigrostriatal dysfunction rather than degeneration of the substantia nigra [7]. However, severe rigidity, dystonia and tremor have been reported in the absence of basal ganglia or substantia nigra damage, and are postulated to reflect damage to the sensorimotor cortex and its extrapyramidal projections [7,18].

The neuropathological substrate of CBS is most commonly a tauopathy, with a subtype of four microtubule-binding repeats (4R-tau) most common, as seen in CBD and PSP pathology. CBS is also associated with TDP-43 pathology, mostly observed in progranulin gene mutation carriers [19,20], although sporadic cases are also reported [21]. Small clinicopathological series have shown a significant proportion of CBS cases with AD pathology: a mixed 3R/4R tauopathy [22]. In one study of 12 CBS cases followed to autopsy, AD pathology represented 50% of CBS and the remaining 50% were CBD [3]. Increasing numbers of case reports [12,23–33] or small case series comprising two to six patients [2,3,7,12,34,35] of CBS-AD have emerged over the past 20 years in the literature, totaling approximately 42 cases. Litvan *et al.* proposed criteria to accurately predict underlying CBD pathology, including limb dystonia, ideomotor apraxia, myoclonus and asymmetric akinetic-rigid syndrome with late-onset gait or balance impairment [36]. However, these clinical features have also been reported with AD pathology [2,3].

Corticobasal pathology compared with AD pathology

The first cases of CBS described by Rebeiz *et al.* in 1968 were associated with a unique underlying pathology, now termed corticobasal degeneration [18]. Current pathologic diagnostic criteria specify tau-positive neuronal and glial lesions in the gray and white cortex and basal ganglia. The abnormal tau protein is hyperphosphorylated and deposited as various inclusions termed astrocytic plaques, thread-like lesions, corticobasal bodies and coiled bodies; swollen or achromatic ballooned neurons are usually present [37]. Frontal or parietal cortices and subcortical regions are typically involved, with relative sparing of the temporal cortex, including the medial temporal cortex. Interestingly, the temporal cortices are the first sites involved in AD, which raises the questions of why and how AD pathology can produce CBS, if topography rather than lesion type is responsible. However, this theory of location of lesion deposition is thought to explain why CBD pathology may produce a variety of clinical phenotypes apart from CBS (e.g., progressive supranuclear palsy syndrome, behavioral variant frontotemporal dementia and apraxia of speech) [7,14].

Alzheimer's disease pathology is the most common cause of dementia in adults. The ascribed clinical picture of DAT is progressive episodic memory loss accompanied by deficits in executive and visuospatial functioning [38]. The key neuropathological findings are loss of neurons and synaptic density, and the deposition of amyloid plaques and neurofibrillary tangles [39]. AD pathology is deposited initially in hippocampal and entorhinal structures, progressing to involve nearby association areas, usually the temporal and parietal association cortices [40]. This histological progression is thought to parallel the clinical progression of DAT. The motor and sensory cortices are almost always spared. However, focal cortical syndromes have been increasingly recognized with AD pathology due to very selective asymmetric disease burden, including CBS, posterior cortical atrophy and primary progressive aphasia [41]. In these cases, AD pathology is highly concentrated in regions typically spared, such as the sensorimotor cortex or parieto-occipital cortex. An interesting and unanswered question is why the pathology is so asymmetric and what drives the tauopathy to selectively target a focal brain site. This is also of interest in CBD pathology, which tends to be very asymmetric, as compared with some other neurodegenerative diseases, such as typical PSP or Lewy body disease, where dramatic asymmetry is not a well-recognized feature [42,43].

Alzheimer's disease has established risk factors. Age is the strongest risk factor, with exponentially increased risk after 65 years of age [44]. Apolipoprotein E (*APOE*) e4 status [45] and a positive family history of AD [46] are also risk factors. By contrast, CBD pathology is believed to be sporadic. Familial cases of CBS are relatively less common and have only been described for frontotemporal dementia with parkinsonism linked to chromosome 17 pathology, a hereditary form of tauopathy with heterozygous tau mutation [47], familial multisystem tauopathy with presenile dementia [48] and in progranulin gene mutations [19,20].

Abnormal tau deposition occurs in both AD and CBD where tau dysfunction affects axonal transport and microtubule stability in neurons. However, tau isoforms differ between AD and CBD depending on whether exon 10 is spliced in (4R) or spliced out (3R). CBD is a 4R tauopathy, while both 3R and 4R abnormal tau is found in AD [49]. Although both AD and CBD are tauopathies, AD also has coexisting β -amyloid protein deposition; a combination that is unique amongst the dementias. Clinical and pathologic overlap amongst the tauopathies has been explained, in part, by differences in the location of the tau protein deposition.

Comparison of CBS-AD to CBS-CBD

Predicting AD pathology in CBS currently remains challenging, although current research is specifically trying to tackle this issue. A major hurdle in evaluating this clinical entity is its rarity and the lack of autopsy studies. In addition, the nomenclature has only recently evolved in the last 5–10 years, to discriminate between clinical syndromes and pathology; previously CBD could imply the clinical syndrome or pathological diagnosis, or both. Thus while neurocognitive and imaging profiles reportedly differ between ‘CBD’ and ‘AD’, this tends to reflect the prototype clinical syndromes without autopsy confirmation of pathology. This article focuses on clinical and imaging features in studies with autopsy-proven CBS-AD compared with CBS-CBD. Identifying tools to better predict AD pathology is of particular relevance because disease-modifying therapies for AD are undergoing various phase clinical trials.

Demographic factors

Hu *et al.* noted that CBS-AD cases in their cohort were younger than CBS-CBD cases [2]. Overall, the age of onset in CBS-AD falls under the time frame of an ‘early-onset AD’, rather than ‘late-onset’, which presents at an age of greater than 65 years. Interestingly, it is early-onset AD that tends to show more rapid progression, generalized cortical deficits, cortical atrophy and hypometabolism compared with late-onset patients of a similar stage [50]. Most studies show that early-onset AD is associated with greater attention, language, praxis, visuospatial and executive dysfunction [51], while late-onset AD is associated with greater impairment in episodic memory. Early-onset AD is typically associated with more severe neuroimaging findings, with increased cortical atrophy, hypoperfusion and hypometabolism, especially in parietal and lateral temporal cortices, versus the medial temporal cortex in late-onset AD; supporting the findings in CBS-AD.

Apolipoprotein E e4 confers an increased risk of AD, but does not account for all cases. Unfortunately, *APOE* e4 has not been well documented in CBS-AD cases to determine any associations. Interestingly, Schneider *et al.* showed that pathologically proven CBS-CBD cases have a higher frequency of the *APOE* e4 allele than controls, although not as high as in AD patients [5]. Thus, *APOE* genotype may not be a useful discriminator of pathology.

MAPT H1 haplotype may be a genetic risk factor for CBD and hence CBS-CBD. The chromosomal region containing the tau gene involves two major haplotypes, H1 and H2, which are defined by linkage disequilibrium between several polymorphisms over the entire gene. There has not been any strong association between the H1 haplotype and AD [52], while an association with CBD was reported [53].

Family history is positive in approximately 25% of AD cases presenting with typical DAT [54]. On the contrary, family history tends to be negative in CBS presentations of AD and in CBS-CBD; therefore, sporadic CBS could indicate either AD or CBD pathology. Unfortunately, family history information was not recorded in some studies.

Several risk factors, including prior head injury, obesity, insulin resistance and vascular risk factors (hypertension, hypercholesterolemia and obstructive sleep apnea), are believed to increase the risk of AD. The role of these risk factors is not known in CBS-AD. More recently, late-life depression, social isolation and lack of physical exercise have been shown to be associated with AD pathology risk, but it is unclear whether these associations also occur in CBS-AD.

Clinical factors

Myoclonus is well established as a feature of AD, but has also been associated with CBD [54]. However, Hu *et al.* noted that it was more common in CBS-AD (four out of five) than CBS-CBD (two out of 11) cases [2]. Shelley *et al.* reported two out of six CBS-AD cases with myoclonus, but no CBS-CBD cases [3]. The presence of myoclonus may, therefore, be more suggestive of CBS-AD than CBS-CBD. Limb apraxia has been reported to occur in both pathologies in approximately equal frequencies. Tremor occurred only within the CBD subgroup in the study by Hu *et al.* [2]. Supranuclear gaze palsy was rarely reported in CBS-AD, but was more common in CBS-CBD. Parkinsonism may point away from CBS-AD, as higher Unified Parkinson's Disease Rating Scale scores were reported in CBS-CBD compared with CBS-AD [55,56].

Neurocognitive factors

Dementia is recognized in CBS, and may be the most common diagnosis in pathologically confirmed CBD, as it is in AD [10]. The cognitive profile probably varies according to the topographical distribution of pathology. For example, left hemisphere involvement may produce a language disorder, while right hemisphere lesion burden produces visuospatial dysfunction. Memory is usually relatively intact in CBS, consistent with relative sparing of the medial temporal cortex in CBD, but as this is the typical location of AD pathology one would anticipate impairment in these cases. Two studies did not report any difference in memory impairment and attentional deficits between CBS-AD and CBS-CBD [2,56]. However, Shelley *et al.* noted that initial episodic memory loss appeared to predict CBS-AD [3]. This was also noted by others [11,26,28]. Supporting this observation, Borroni *et al.* recently reported early memory impairment in CBS cases with an AD pathology bioprofile (cerebrospinal fluid [CSF] and SPECT imaging consistent with AD), compared with CBS cases with a non-AD profile [57].

It has been noted that frontal lobe symptoms (utilization behavior, personality change and frontal release signs) are associated with CBS-CBD [3,5,11]. Neuropsychometric evaluation of frontal lobe involvement and dysexecutive function may thus help identify CBS-CBD [58,59]. Indeed, verbal letter and category fluency testing are abnormal in CBD [60,61]. Agrammatic aphasia and orobuccal apraxia has also been associated with CBS-CBD [3,56,61], although language can remain preserved [23,28]. Conversely, visuospatial impairment may indicate CBS-AD; Alladi *et al.* reported visuospatial impairment in six out of six cases [11] and Ceccaldi *et al.* in two out of two [34], although it was found in both CBS-AD and CBS-CBD in the Whitwell *et al.* series [56]. These findings emphasize that frontal disease distribution and less involvement of the medial temporal lobe are correlated with CBS-CBD, while impairment in parietal lobe function is associated with CBS-AD.

Biochemical markers

Biochemical markers for AD that reflect cortical pathology, including neuronal degeneration, β -amyloid plaque deposition and tau hyperphosphorylation, are currently under extensive research. Serum biomarkers have thus far proved disappointing with no consensus, and verification is waiting [62]. CSF biomarkers appear promising. A decline in $A\beta_{42}$ increase in total tau (t-tau) and phosphorylated tau (p-tau) and ratio of low $A\beta_{42}$:high tau is characteristic for AD [63]. The combined sensitivity and specificity is 80–90% when comparing AD to controls, although overlap occurs. Low $A\beta_{42}$ and ratio of p-tau: $A\beta_{42}$ in CSF has a high predictive value for AD pathology [64,65]. Therefore, CSF biomarkers may be a useful as amyloid-labeled imaging in predicting AD in patients presenting with CBS.

Neuroimaging markers

Much research has correlated anatomical and functional imaging with CBS and DAT, and found specific patterns of atrophy or altered metabolism, respectively. However, the caveat again is that there are very few studies with autopsy-proven diagnosis of CBD or AD, thus these findings are limited in predicting an underlying pathology for CBS. However, one may surmise that perhaps there may be features of AD on antemortem scans in the setting of CBS that may hint at this pathology. Autopsy-proven pathological case series will be required to confirm this hypothesis.

MRI

Typical MRI findings in CBS are asymmetric cortical atrophy, mainly frontoparietal, with the most severe changes contralateral to the more affected clinical side [66,67]. This pattern of atrophy is sensitive to CBS diagnosis, but not specific to any particular underlying pathology [68]. By comparison, the medial temporal lobes, especially the hippocampus and entorhinal cortex, are amongst the earliest site of pathologic involvement in AD, reflected by reduced hippocampal and entorhinal cortex volumes on brain MRI compared with age-matched controls. Cortical volume loss in AD is usually extensive and involves frontal, temporal and parietal lobes [69,70]. Thus one could postulate that widespread MRI patterns of atrophy may predict AD pathology. Supporting this, diffuse atrophy was noted in several CBS-AD cases [24,28,29].

Voxel-based morphology (VBM) uses group analysis to evaluate regional brain atrophy without any *a priori* assumptions. Whitwell *et al.* examined CBS cases with various autopsy-proven pathologies, and found the only common site of involvement was the premotor cortex and insula (dominant) and supplementary motor area (dominant and nondominant) [56]. The patterns of atrophy were relatively restricted to inferior and superior posterior frontal regions in CBS-CBD, but were more widespread in CBS-AD, with additional involvement of the temporoparietal lobes [55,56]. Therefore, a more widespread and posterior pattern of atrophy is associated with CBS-AD. Interestingly, both CBS-CBD and CBS-AD showed relative sparing of the hippocampus, typical for CBD pathology but atypical for AD pathology [55,56] (Figure 1). These patterns of atrophy may, therefore, be useful to help predict pathology in subjects with CBS.

Temporoparietal atrophy has also been shown to be a sensitive and specific marker of AD pathology in a study assessing autopsy-proven AD and non-AD pathology cases that underwent VBM [71]. Rates of brain atrophy may also be a helpful discriminator for AD pathology versus CBD pathology in CBS, since rates of atrophy in CBD have been shown to be faster than that of AD [72].

Functional imaging with resting state MRI

Resting state functional MRI (fMRI) demonstrates reduced activity in AD in the default mode network, encompassing the posterior cingulate, inferior parietal, inferolateral temporal, ventral anterior cingulate and hippocampus [73,74]. This is consistent with typical structural imaging for AD. There are no published studies as yet assessing resting state fMRI in pathologically confirmed cases of AD, or comparing CBD to AD.

SPECT

SPECT imaging studies appear promising. Asymmetric hypoperfusion in frontoparietal lobes and basal ganglia is reportedly common in CBS [66,75]. By comparison, the AD hypoperfusion pattern in autopsy-proven cases involves the parietal and temporal lobes, precuneus and posterior cingulate cortex [76,77]. SPECT parietal lobe hypoperfusion may be more associated with CBS-AD than CBS-CBD [2]. Furthermore, CBS cases with a CSF

AD profile had SPECT images that also resembled AD, with greater hypoperfusion in the precuneus, posterior cingulate and bilateral hippocampi [57].

Fluorodeoxyglucose-PET

Glucose hypometabolism in the precuneus, posterior cingulate and biparietal regions is observed in AD. This correlates with elevated CSF t-tau and p-tau and reduced metabolism. By comparison, CBS typically has asymmetric hypoperfusion within the parietofrontal cortex and basal ganglia [78,79], although PET findings in pathologically proven CBD are rarely reported. Asymmetric hypometabolism in the contralateral frontoparietal cortex, basal ganglia and cerebellum has been reported [14]. A recent radiological study found that fluorodeoxyglucose-PET scans performed early can predict clinical syndromes that later meet diagnostic criteria. Disease-specific patterns of relatively decreased metabolic activity were found in CBS (contralateral cortical regions) and AD (parietotemporal regions); however, they were not pathologically confirmed [80]. If this was supported by autopsy studies, then early PET in CBS could be helpful to predict the underlying pathology.

Amyloid PET imaging

This powerful new imaging technique uses ligands that attach to fibrillar amyloid, such as Pittsburgh compound B (PiB), flor-betaben and AV-45 [62], and allows the detection of amyloid in the brain during life. Widespread use of this modality is restricted by requirements for an on-site cyclotron and radiochemistry laboratory. However, PiB has been shown to be sensitive and specific for amyloid deposition, and has been reliably demonstrated to differentiate AD from FTD. It can also differentiate AD from normal controls, although some normal elderly patients may have positive findings due to age-related amyloid deposition [81]. No comparisons with CBD have yet been reported.

Literature summary of CBS-AD compared with CBS-CBD cases

To determine whether any of the discussed demographic or clinical factors may be useful predictors of pathology, a literature summary was compiled for all cases published up to 30 May 2011, in the literature of CBS-AD compared with CBS-CBD cases. A PubMed search with the terms “corticobasal syndrome” or “corticobasal degeneration”, cross-matched with “Alzheimer’s disease” was employed to identify all cases of CBS-AD and CBS-CBD. Approximately 42 cases of CBS-AD were either published as case reports or small case series [2,3,7,11,12,23–33,35,55,56,82,83]. Duplicate cases or cases with coexistent pathology with AD were excluded where these could be determined. Cases were included (n = 29) only if there was sufficient detail to include demographic, clinical, imaging and pathologic information to compile a literature summary. These were compared with CBS-CBD cases (n = 24) to identify clinical or imaging differences that could increase the antemortem diagnosis of AD. Given the number of variables assessed, we consider $p < 0.01$ as significant. Continuous variables were compared using Mann–Whitney U test and categorical variables were assessed using χ^2 test.

Comparing 29 CBS-AD to 24 CBS-CBD cases, there were several key findings that appeared to be associated with AD pathology (Table 1): longer disease duration, younger age at onset, hemisensory neglect, memory impairment, visuospatial difficulties, dressing apraxia and myoclonus. Importantly, there was no difference between aphasia, limb apraxia, alien limb phenomenon, fisted hand, parkinsonism, pyramidal motor signs, dystonia or Gerstmann syndrome. This is not surprising given that both subgroups had the same clinical diagnosis of CBS, of which these signs meet inclusion criteria. Perhaps of more interest, there was no difference in change of gait (which is usually normal in typical AD), aphasia (as observed by several small group studies) or personality change or frontal release signs (anticipated for CBD). There were no significant associations with CBS-CBD, although we

noted a trend for utilization behavior, rigidity and extraocular dysfunction to be associated with CBS-CBD. These findings are not surprising given that imaging demonstrates focal frontal lobe atrophy in CBS-CBD, compared with more parietal lobe findings in CBS-AD. Family history was recorded in too few cases to compare with confidence. Overall these findings are of interest, and require confirmation in larger prospective studies. It will also be important to identify whether a combination of clinical features is most sensitive and specific for CBS-AD.

The findings from this literature review should be considered hypothesis generating as many studies are limited by the absence of well-designed prospective protocols utilizing standardized and validated tests. This is important since some of the signs reported may not have been properly characterized. Memory impairment, for example, will need to be operationally defined with a verbal serial list-learning test comprised of three elements: very low performance on delay-free recall; random or near random performance on a delayed recognition test; and the production of extra-list intrusion errors. Aphasia should be better defined and the presence or absence of apraxia of speech included. Limb apraxia should also be separated into anterior versus posterior limb apraxia. Therefore, it is important to assess other cognitive domains. Memory impairment in CBS-CBD, for example, is often confined to visual memory [84], a finding that may be confounded by visuospatial impairment, although the underlying nature of the visuospatial impairment is controversial.

It should be noted that since the completion of this literature review another CBS study with pathology has been published with results supporting many of the findings reported in this article [85].

Expert commentary

Clinicopathological studies have now clearly demonstrated that CBS, as currently defined, is nonspecific, with an increasing number of reports showing AD pathology underlying the syndrome. Differentiating CBS-AD from CBS-CBD based solely on clinical features has not been possible. Given that recent evidence from VBM studies showing that CBS-CBD is associated with posterior frontal atrophy while CBS-AD is associated with more widespread atrophy, particularly involving the parietal lobes, symptoms associated with parietal lobe dysfunction should predict CBS-AD (Box 1). However, more promising to differentiate CBS-CBD from CBS-AD, are CSF and amyloid imaging biomarkers, although neither would allow us to predict dual pathologies.

Box 1

Clinical, cerebral spinal fluid and imaging signs suggestive of Alzheimer's disease pathology in corticobasal syndrome

Clinical signs

- Longer disease duration (compared with CBD pathology)
- Limb myoclonus
- Dressing apraxia
- Memory loss
- Lower MMSE on presentation
- Cortical sensory loss
- Visuospatial difficulties

- Hemisensory neglect
- Absence of limb rigidity

Cerebral spinal fluid signs

A β 42 reduction, and elevated total and phosphorylated tau

Imaging signs

- MRI: posterior lateral temporoparietal atrophy
- FDG-PET: temporoparietal hypometabolism
- C11-PiB-PET positive amyloid imaging

A β : Amyloid β ; CBD: Corticobasal degeneration; FDG: Fluorodeoxyglucose; MMSE: Mini-Mental State Examination; PiB: Pittsburgh compound B ([N-methyl-¹¹C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole).

Five-year view

One would anticipate that future research will aim to improve pathologic diagnostic accuracy for all neurodegenerative diseases, spurred on by the development of disease-modifying agents. Clinical diagnosis of CBS, coupled with improved imaging techniques and biomarkers, should help to identify underlying AD pathology. To refine the clinicopathological diagnosis of CBS-AD, the gold standard would be prospective recruitment of CBS cases as a multicenter study, collecting CSF biomarkers and performing periodic anatomical, functional and amyloid-labeled imaging, with autopsy follow-up for pathologic confirmation to better define which investigations aid the diagnosis. Borroni *et al.*'s recently published study is employing some of these very techniques to try to predict AD pathology in CBS cases, although autopsy confirmation is not included [57]. Future imaging developments that could label both 3R and 4R tau *in vivo* in order to suggest AD pathology, rather than a pure 4R tauopathy, such as CBD, would be useful.

Early diagnosis of CBS-AD would allow therapeutic agents, such as cholinesterase inhibitors or NMDA receptor antagonists to be potentially employed for benefit, although at present there is no evidence that these therapies will be helpful in CBS-AD. CBS cases cannot be treated empirically as therapies have side effects. Of importance, early identification of AD could lead to early utility of disease-modifying agents to slow AD-associated neurodegeneration. For example, reducing amyloid burden via β -secretase or γ -secretase inhibitors, amyloid monoclonal antibodies or amyloid anti-aggregation therapies, or reducing tau deposition or improving stability via tau microtubule stabilizers. Response to therapy could be tracked through these very biomarkers.

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Key issues

- Corticobasal syndrome (CBS) is a rare neurodegenerative disorder characterized by asymmetrical cortical and extrapyramidal dysfunction.
- Although the CBS was initially thought to be specific to a single pathology, it is increasingly recognized that the syndrome is nonspecific to any one pathology.
- Many pathologies underlie the corticobasal syndrome, including corticobasal degeneration (CBD) and Alzheimer's disease (AD).
- Both CBD and AD are considered tauopathies; however, CBD is a four microtubule-binding repeats tauopathy, while AD is a three microtubule-binding repeats and four microtubule-binding repeats tauopathy.
- Clinical studies have not been able to differentiate AD from CBD when they underlie the corticobasal syndrome.
- Imaging studies have demonstrated that CBS-CBD is characterized by relatively focal posterior frontal (premotor) atrophy, while CBS-AD shows more widespread frontal and parietal atrophy.
- This literature review has identified clinical features that appear to be associated with CBS-AD, including myoclonus, visuospatial deficits, memory impairment, dressing apraxia, hemisensory neglect and younger age at onset.
- No features were significantly associated with CBS-CBD, although there was some suggestion of association with utilization behavior and ocular motor impairment.
- Amyloid imaging and cerebrospinal fluid biomarkers show promise as potential biomarkers to differentiate CBS-CBD from CBS-AD.

Figure 1. Voxel-based morphometry results showing patterns of gray matter loss in six subjects with corticobasal syndrome with corticobasal degeneration and five subjects with corticobasal syndrome with Alzheimer's disease compared with 20 age- and gender-matched controls
 The CBS-AD subjects were more highly educated and younger than the CBS-CBD subjects. Age and gender were included as covariates in the model. Results are shown on transparent renders of the brain at a statistical threshold of $p < 0.001$ uncorrected for multiple comparisons. AD: Alzheimer's disease; CBD: Corticobasal degeneration; CBS: Corticobasal syndrome; L: Left; R: Right.

Table 1

Comparison of demographics and clinical features of corticobasal syndrome with underlying Alzheimer's disease pathology and corticobasal syndrome with underlying corticobasal degeneration.

Demographic and clinical features	CBS-AD (n = 29), positive cases/total cases recorded (%)	CBS-CBD (n = 24) (%)	p-value
Gender (males)	12/29 (41)	10/24 (42)	0.98
Right-handed	22/23 (96)	13/14 (93)	0.72
Age of onset (years)	60 (50–75) (n = 29)	66 (41–73) (n = 24)	0.003
Disease duration (years) [†]	9 (3–22) (n = 27)	6 (3–11) (n = 24)	0.0006
Age at death (years) [†]	68 (61–88) (n = 26)	72 (47–84) (n = 24)	0.23
Left side of onset	19/26 (73)	12/24 (50)	0.18
<i>Cortical</i>			
Apraxia (nonspecified)	27/27 (100)	23/24 (96)	0.22
Alien limb	9/13 (69)	7/13 (54)	0.42
Aphasia	9/22 (41)	12/20 (60)	0.22
Memory impairment	21/25 (84)	10/24 (42)	0.002
Dressing apraxia	12/12 (100)	4/7 (57)	0.008
Personality/behavior change	7/18 (39)	8/13 (62)	0.21
Cortical sensory loss	12/17 (71)	8/21 (38)	0.04
Visuospatial disturbance	12/20 (60)	2/13 (15)	0.009
Utilization behavior	0/8 (0)	3/6 (50)	0.01
Constructional apraxia	10/10 (100)	5/7 (71)	0.04
MMSE on presentation [†]	16 (9–23)	22 (20–27)	0.04
Gerstmann's syndrome	2/3 (67)	3/7 (43)	0.49
Hemisensory neglect	8/8 (100)	3/7 (43)	0.005
Frontal release signs	15/22 (68)	11/20 (55)	0.38
<i>Motor</i>			
Extraocular disturbance	5/17 (29)	15/24 (63)	0.04
Parkinsonism	15/17 (88)	16/17 (94)	0.54
Bradykinesia	5/5 (100)	10/11 (91)	0.38
Rigidity	12/15 (80)	18/18 (100)	0.02
Dystonia	8/21 (38)	10/20 (50)	0.44
Tremor	5/6 (83)	10/11 (91)	0.65
Myoclonus	17/23 (74)	4/20 (20)	0.0003
Postural instability/gait change	9/20 (45)	16/24 (67)	0.15
Fisted hand	3/3 (100)	5/7 (71)	0.20
Dysarthria	4/9 (44)	5/13 (38)	0.78
Dysphagia	4/10 (40)	3/6 (50)	0.70
Pyramidal signs	9/10 (90)	4/7 (57)	0.11

[†] Data shown as median (range).

CBS-AD: Corticobasal syndrome with Alzheimer's disease pathology; CBS-CBD: Corticobasal syndrome with underlying corticobasal degeneration; MMSE: Mini-Mental State Examination.