Neuropathology and emerging biomarkers in corticobasal syndrome

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ABSTRACT
Corticobasal syndrome (CBS) is a clinical syndrome characterised by progressive asymmetric limb rigidity and apraxia with dystonia, myoclonus, cortical sensory loss and alien limb phenomenon. Corticobasal degeneration (CBD) is one of the most common underlying pathologies of CBS, but other disorders, such as progressive supranuclear palsy (PSP), Alzheimer’s disease (AD), and frontotemporal lobar degeneration with TDP-43 inclusions, are also associated with this syndrome. In this review, we describe common and rare neuropathological findings in CBS, including tauopathies, synucleinopathies, TDP-43 proteinopathies, fused in sarcoma proteinopathy, prion disease (Creutzfeldt-Jakob disease) and cerebrovascular disease, based on a narrative review of the literature and clinicopathological studies from two brain banks. Genetic mutations associated with CBS, including GRN and MAPT, are also reviewed. Clinicopathological studies on neurodegenerative disorders associated with CBS have shown that regardless of the underlying pathology, frontoparietal, as well as motor and premotor pathology is associated with CBS. Clinical features that can predict the underlying pathology of CBS remain unclear. Using AD-related biomarkers (ie, amyloid and tau positron emission tomography (PET) and fluid biomarkers), CBS caused by AD often can be differentiated from other causes of CBS. Tau PET may help distinguish AD from other tauopathies and non-tauopathies, but it remains challenging to differentiate non-AD tauopathies, especially PSP and CBD. Although the current clinical diagnostic criteria for CBS have suboptimal sensitivity and specificity, emerging biomarkers hold promise for future improvements in the diagnosis of underlying pathology in patients with CBS.

INTRODUCTION
Corticobasal degeneration (CBD) is a progressive neurodegenerative tauopathy presenting with asymmetric rigidity, apraxia, dystonia, myoclonus, cortical sensory loss and dystonia, as well as behavioural and cognitive impairment such as aphasia. It has been increasingly recognised that other disorders, such as progressive supranuclear palsy (PSP) and Alzheimer’s disease (AD), can present with characteristic features that mimic CBD. Boeve et al investigated the postmortem neuropathology of 13 patients who were thought to have CBD based on clinical criteria and found that only 7 patients (54%) had neuropathological findings of CBD (figure 1). Other pathological diagnoses were AD in two patients, PSP, Pick’s disease, Creutzfeldt-Jakob disease (CJD) and non-specific degenerative changes. They considered that characteristic clinical features were explained by the topographical distribution of lesions, regardless of the underlying pathology. Subsequently, Cordato et al coined the term ‘corticobasal syndrome’ (CBS) to refer to the shared clinical features of six patients, four of whom at postmortem evaluation had CBD; the other two had PSP. Subsequently, Boeve et al proposed that CBD be limited to the neuropathological disorder, while CBS should be used to refer to the clinical syndrome of progressive asymmetric rigidity and apraxia.

DIAGNOSTIC CRITERIA FOR CBS
Various diagnostic criteria for CBS have been proposed. Progressive, asymmetric akinetic rigid syndrome with apraxia is a feature in all criteria, but cognitive impairment, including aphasia, is included in some criteria (figure 2). The Mayo Clinic criteria include apraxia of speech/non-fluent aphasia as one of the core features, while frontal dysfunction was considered a supportive feature. The University of Toronto criteria do not include cognitive or language impairment. The modified Cambridge criteria have greater emphasis on cognitive and language dysfunction, including aphasia, executive dysfunction and visuospatial dysfunction. Criteria proposed by a group of international experts, including data from unpublished autopsy series, were reported by Armstrong et al. In these criteria, four clinical phenotypes of CBD are proposed: CBS, PSP syndrome, fronto-behavioral-spatial syndrome and non-fluent/agrammatic variant of primary progressive aphasia. CBS is further classified as probable or possible. Probable CBS requires asymmetric motor signs, while possible CBS could have symmetric motor signs. Based on the combination of clinical phenotypes and other features, two degrees of certainty are defined in the Armstrong criteria—clinically probable CBD and clinically possible CBD. The former aimed to identify CBD without significant other pathology, while the latter would include cases that might have other (ie, mixed) pathology. Although it was recognised that some patients with autopsy-proven CBD can present with AD-type dementia, this clinical phenotype was excluded from the criteria. The significant advance in the Armstrong criteria is that it includes clinical phenotypes other than...
CBS. Subsequent clinicopathological studies have shown that the sensitivity and specificity of the Armstrong criteria are suboptimal.\textsuperscript{10}

More recently, the International Parkinson and Movement Disorder Society (MDS) proposed diagnostic criteria for PSP, which include eight clinical phenotypes for PSP, including CBS (possible PSP-CBS).\textsuperscript{3} This clinical phenotype is considered a probable 4-repeat (4R)-taupathy, which has a high likelihood of underlying PSP or CBD pathology. The MDS criteria include AD-related biomarkers to exclude primary AD pathology from PSP-CBS, but they did not adopt tau positron emission tomography (PET) to detect PSP pathology. With development of molecular biomarkers for amyloid-\beta and tau, it will be necessary to incorporate these into diagnostic criteria to achieve optimal sensitivity and specificity.

**NEUROPATHOLOGY OF CBS**

Heterogeneity of the underlying neuropathology associated with CBS has been reported in several autopsy series.\textsuperscript{2,4,11,12} Figure 1 summarises the frequency of the underlying pathology of CBS reported from the USA, UK and Japan, including unpublished data from two brain banks at the Institute for Medical Science of Aging, Aichi Medical University (1994–2020) and Mayo Clinic Florida (1998–2021). CBD accounted for less than half of patients with CBS, while PSP and AD were the most common non-CBD pathological diagnoses.\textsuperscript{11,12} Other neuropathological findings in patients with CBS were Lewy body disease (LBD).\textsuperscript{13} frontotemporal lobar degeneration (FTLD) with TDP-43 inclusions (FTLD-TDP),\textsuperscript{14} motor neuron disease,\textsuperscript{15} FTLD with fused-in-sarcoma pathology (FTLD-FUS),\textsuperscript{16} cerebrovascular disease,\textsuperscript{17} CJD\textsuperscript{18} and atypical multiple system atrophy (MSA).\textsuperscript{19}

As of November 2021, the Mayo Clinic brain bank for neurodegenerative disorders has 345 brains from patients with an antemortem diagnosis of CBS. This clinical diagnosis is based on the final evaluation by clinicians who saw the patient later in the disease course. Rigorous clinical diagnostic criteria were not always applied, and not all patients were longitudinally followed by movement disorders specialists; therefore, the certainty of clinical diagnoses varies. The most common pathological diagnoses were CBD (32%), followed by PSP (31%), AD (20%) and others (17%), including LBD, FTLD-TDP, motor neuron disease, Pick’s disease, FTLD-FUS, CJD and cerebrovascular disease (figure 1).

In the following section, we will discuss clinicopathological features and genetic correlates of the disorders that can present with CBS, including tauopathies, synucleinopathies, TDP-43 proteinopathies, FUS proteinopathy, CJD and cerebrovascular disease (figure 3).\textsuperscript{20}

**Tauopathies**

Tauopathy, a collective term for neurodegenerative disorders characterised by accumulation of hyperphosphorylated tau proteins in neurons and glia,\textsuperscript{21} is the most common pathology associated with CBS. Tau protein, encoded by the MAPT gene, has six tau isoforms in adult brains. Alternative splicing of exon 10 in MAPT gene gives rise to 3-repeat (3R) or 4R tau.\textsuperscript{22} The tau isoforms in CBD, PSP and globular glial tauopathy (GGT) are primarily composed of 4R tau, hence these disorders are categorised as 4R tauopathies. Pick’s disease is a 3R tauopathy. All six tau isoforms are found in AD; thus, AD is a mixed 3R/4R tauopathy.

| Neurodegeneration | Neuronal group | Disease category | Clinical manifestation | Genetic factor |
|-------------------|----------------|-----------------|----------------------|---------------|
| CBS | Corticobasal syndrome | FBS, CBD, FTLD | Dysphagia, apraxia, rigidity, bradykinesia | MAPT, TAR, FUS |
| PSP | Progressive supranuclear palsy syndrome | Motor neuron disease | Ophthalmoplegia, axial rigidity, parkinsonism | MAPT, TAR, FUS |
| AD | Alzheimer’s disease | AD | Memory loss, cognitive decline | APOE, MAPT, TAR |

Figure 1: Frequency of the common underlying pathologies associated with CBS. The pie charts (not drawn to scale) on the upper row are from review of the literature.\textsuperscript{2,11,12} The pie charts on the lower row are from unpublished data from the brain bank at the Institute for Medical Science of Aging, Aichi Medical University (1994–2020) and the Mayo Clinic brain bank (1998–2021). CBD is the most frequent underlying pathology, followed by PSP and AD. AD, Alzheimer’s disease; CBD, corticobasal degeneration; CBS, corticobasal syndrome; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 inclusions; PSP, progressive supranuclear palsy.

Figure 2: Comparison of diagnostic criteria for CBS. Five commonly used criteria for CBS are compared. The motor symptoms and signs are included in common in CBS, but the cognitive and language impairment are different in Mayo Clinic criteria, University of Toronto criteria and the modified Cambridge criteria.\textsuperscript{6-8} Armstrong criteria define four clinical presentations in CBD.\textsuperscript{7} The CBS of the modified Cambridge criteria roughly corresponds to CBS, PNFA and FBS of the Armstrong criteria. The MDS diagnostic criteria for PSP define PSP-CBS, which partially overlaps PSP syndrome of Armstrong criteria, although dystonia is not included in the criteria for PSP-CBS.\textsuperscript{6} Both Armstrong and MDS criteria list exclusion criteria, which suggest other underlying pathology. CBS, corticobasal syndrome; FBS, frontobrachial-spatial syndrome; MDS, International Parkinson and Movement Disorder Society; PNFA, progressive non-fluent aphasia; PSPS, progressive supranuclear palsy syndrome.
Corticobasal degeneration

CBD is characterised by tau aggregates in neurons and glia in both cortical and subcortical regions. Macroscopically, atrophy in the medial surface of the superior frontal gyrus, thinning of the corpus callosum, subcortical white matter atrophy and discolouration of the globus pallidus are typical findings in patients with CBS (figure 4A,B). Atrophy may be asymmetric, but the lack of marked asymmetry does not rule out CBD. The thalamic nucleus may have atrophy, but it is less affected than in PSP. A variable degree of loss of pigment in the substantia nigra is observed. In contrast, loss of pigment in the locus coeruleus is less consistent, which differs from LBD and AD. On microscopic examination, spongiosis in the superficial layers and balloon neurons in the lower cortical layers are often seen in affected neocortices. Rarefaction of subcortical white matter, including U-fibres, is a characteristic feature of CBD. The pathognomonic features of CBD are astrocytic plaques in grey matter (figure 4C) and numerous threads in both grey and white matter (figure 4D). Pretangles are more prominent than mature neurofibrillary tangles, which is different from tau pathology in AD and PSP (figure 4E). Astrocytic plaques are usually frequent in the neostriatum, although neuronal loss is relatively mild in this region compared with the globus pallidus and substantia nigra.

Pathologically, CBD can be divided into three subtypes on the basis of the distribution and severity of the lesions: typical CBD, ‘basal ganglia predominant CBD’ and ‘PSP-like CBD’. These subtypes correspond well to clinical phenotypes. Typical CBD is associated with CBS or frontal behavioural-spatial syndrome. ‘Basal ganglia predominant’ and ‘PSP-like’ CBD are associated with PSP syndrome. Another study reported that CBD-CBS had a greater tau burden in the frontal and parietal cortices, including the motor cortex, than CBD presenting as PSP (ie, Richardson syndrome—RS), CBD-RS. In contrast, tau burden in the cerebellum and medulla was greater in CBD-RS than in CBD-CBS. These findings suggest that the distribution of tau pathology differs between the two major clinical presentations of CBD (ie, CBS and RS). The presence of additional pathological processes may also affect clinical phenotypes. For example, TDP-43 pathology, which occurs commonly in elderly individuals, is more frequent in CBD-RS than CBD-CBS with the midbrain tegmentum being most commonly affected, although there was not a clear difference in age between the two groups. Another study demonstrated the correlation between the severity of TDP-43 pathology and neuronal loss in CBD, although the association with the clinical syndrome was not confirmed.

Progressive supranuclear palsy

PSF is also a 4R tauopathy characterised by neuronal and glial tau aggregates predominantly in the subcortical regions. In typical PSF, macroscopic findings of the brain include atrophy of the subthalamic nucleus, midbrain, superior cerebellar peduncle and dentate nucleus. Most PSP patients had at least mild to moderate loss of pigment in substantia nigra. In PSF presenting as CBS (PSP-CBS), macroscopic findings are similar to those of CBD-CBS; namely, atrophy in the superior frontal gyrus, thinning of the corpus callosum and relative preservation of the subthalamic nucleus (figure 4E,F,G). In contrast to astrocytic plaques in CBD, the hallmark pathological glial lesion in PSF is the tufted astrocyte (figure 4H). Coiled bodies (figure 4I) and globose tangles (figure 4J) are also more frequent in PSF than in CBD.

Several clinical phenotypes of autopsy-confirmed PSP have been described. The most recent criteria proposed by the MDS define eight major clinical phenotypes. In addition to RS, which is the typical phenotype characterised by postural instability with early falls and supranuclear gaze palsy, seven atypical clinical phenotypes are proposed. Although PSP is the second most common underlying pathology of CBS, CBS is a relatively rare clinical presentation of PSP—in the range of 4%–9%. As in CBD, differences in clinical phenotypes in PSF can be explained by relative distributions of neurodegeneration and tau pathology. Compared with PSP-RS, PSP-CBS has greater tau...
burden in the middle frontal and inferior parietal cortices. A subsequent study validated this finding, showing increased tau burden in the frontal grey matter and parietal white matter as well as reduced tau burden in the caudate nucleus, subthalamic nucleus and cerebellar white matter in PSP-CBS. A recent study using cryogenic electron microscopy has revealed distinct ultrastructure characteristics of tau filaments in various tauopathies, such as PSP, CBD, GGT and Pick’s disease. Interestingly, however, tau filaments from different PSP subtypes (ie, PSP-RS, PSP-CBS, PSP with predominant parkinsonism and PSP with predominant frontal presentation) were identical, suggesting that distinct clinical phenotypes were not due to different tau filament structure, but rather distribution of the pathology.

Ling et al studied clinical features of CBS with various underlying pathologies and found that the mean duration between onset of vertical supranuclear gaze palsy and the first cardinal symptom was shorter in PSP-CBS than CBD-CBS (2.2 vs 5.9 years). Apraxia of eyelid opening was observed in 3 of 6 PSP-CBS patients, but in none of the patients with CBD-CBS. Lee et al also compared clinical features of CBS with various underlying pathologies, but they could not find any clinical features that were significantly different between the pathological groups.

Both CBD and PSP share genetic risk factors, such as MAPT H1 haplotype. Interestingly, the frequency of homozygous MAPT H1c alleles, a risk subhaplotype of both CBD and PSP, was higher in PSP-CBS than in CBD-CBS. Another study, however, did not find strong associations between MAPT H1c and clinical-pathological features of CBD.

**Alzheimer’s disease**

Since genes that cause familial AD, such as amyloid precursor protein (APP) and presenilin (PSEN), drive amyloid deposits in the brain, not tau pathology, AD is considered to be a secondary tauopathy. AD can be divided into at least three neuropathological subtypes based on the relative distribution of neurofibrillary tangles in the hippocampus and neocortices: typical, hippocampal-sparing and limbic-predominant types. Using tau PET imaging, a fourth subtype—asymmetrical AD—has recently been reported. Hippocampal sparing AD is associated with young age of onset and high frequency of non-amnestic clinical syndrome, such as logopenic variant of primary progressive aphasia, posterior cortical syndrome and CBS. Macroscopic findings of AD associated with CBS are characterised by focal atrophy in the motor cortex and superior frontal gyrus (figure 4K, L). Pathological hallmarks of AD are senile plaques composed of amyloid-β and neurofibrillary tangles composed of hyperphosphorylated tau protein (figure 4M–O).

One study reported that 3.5% of AD patients presented as CBS (AD-CBS). AD-CBS had greater atrophy in the motor cortex and more neuronal loss in the substantia nigra compared with amnestic type AD. Tau burden in the motor cortex was greater in AD-CBS than in amnestic type AD.

Several studies have investigated clinical features that differentiate CBD from AD by comparing clinical features of AD-CBS and CBD-CBS. The age of onset tends to be younger in AD-CBS than CBD-CBS. Data from the Mayo Clinic brain bank supports this finding; the age at onset is significantly younger in AD-CBS than CBD-CBS or PSP-CBS (59 vs 63 vs 70 years; p<0.001). Myoclonus was more frequent in AD-CBS than CBD-CBS in one study, but others did not replicate this finding. Tremor was more frequent in CBD-CBS than in AD-CBS in one study, but another study did not show a significant difference. Only one study compared the frequency of visual neglect, which was more common in AD-CBS. It is challenging to predict the underlying pathology of CBS based solely on clinical features, but molecular biomarkers may help differentiate AD from other aetiologies (see below). In rare cases, familial CBS is caused by mutations associated with early-onset AD, such as PSEN1 and APP.

**Pick’s disease**

Pick’s disease is a 3R tauopathy often characterised by severe circumscribed atrophy (‘knife-edge’ atrophy) in the frontal and temporal lobes. Prominent neuronal loss with gliosis is observed in affected cortices, and some of the remaining neurons are swollen and chromatolytic, so-called Pick cells. Immuno-histochemistry for phosphorylated-tau or 3R-tau shows highly characteristic round neuronal cytoplasmic inclusions (Pick bodies). Pick bodies are often numerous in the dentate gyrus of the hippocampus, as well as the amygdala, frontal and temporal neocortices, and subcortical nuclei, especially the corpus striatum. The most common clinical presentation of Pick’s disease is behavioural variant frontotemporal dementia (bvFTD), but progressive non-fluent aphasia and semantic dementia are also reported. A few case reports have described patients presenting as CBS with underlying pathology of Pick’s disease with or without concomitant AD pathology. One of these patients showed severe focal atrophy of the frontal and parietal lobes, especially around the left central sulcus, while anterior temporal cortices showed relatively mild atrophy. In a recent study, 5 of 21 patients with Pick’s disease (24%) had a clinical diagnosis of CBS, suggesting that CBS may not be a rare presentation of Pick’s disease. Further clinicopathological studies are warranted to determine whether sparing of temporal cortices is a pattern that correlates with the clinical presentation of CBS.

**Globular glial tauopathy**

GGT is an extremely rare 4R tauopathy characterised by 4R-tau-positive globular inclusions in oligodendrocytes and astrocytes. The distribution of tau pathology divides GGT into three pathological subtypes. Type I involves the prefrontal and temporal cortices; type II involves both the motor cortex and the corticospinal tracts; and type III involves the prefrontal, temporal, and motor cortices, and the corticospinal tracts. In a clinicopathological study of 11 GGT patients, the most common clinical diagnosis was bvFTD. Only one patient had CBS with no obvious pyramidal signs. Clinical diagnostic criteria for GGT are not established; therefore, the diagnosis of GGT can be made only by pathological assessment. In this sense, it is currently impossible to predict GGT pathology in patients with CBS.

**MAPT mutations**

To date, more than 70 MAPT mutations or variants have been reported to cause various types of tau pathologies, including CBD, Pick’s disease, GGT and ‘unclassifiable’ tauopathies. Each tauopathy is heterogeneous in clinical presentations and can present as CBS. Common clinical presentations in MAPT mutations are parkinsonism and dementia; hence, the name FTD and parkinsonism linked to chromosome 17. Many cases are familial, but seemingly sporadic patients have been described with MAPT mutations. MAPT p.P301S mutation was first reported in a family with early-onset FTD with parkinsonism, but later reported to cause early-onset CBS (ie, 20s and 30s years old) in several patients. None of the patients with CBS due to this mutation had autopsy confirmation. MAPT p.P301L mutation was also initially reported...
in several families with FTD with parkinsonism.\textsuperscript{65} \textsuperscript{66} One study reported a patient with CBS, but lacked autopsy confirmation.\textsuperscript{67} MAPT p.V363I mutation has been reported to cause bvFTD, non-fluent PPA, posterior cortical atrophy and rarely CBS.\textsuperscript{68}–\textsuperscript{70} Two patients with MAPT p.V363I mutation were identified by screening of 173 CBS patients for tau mutations.\textsuperscript{71} Pathological assessment was performed in one patient, which confirmed CBD-like pathology.\textsuperscript{71} MAPT p.N410H mutation was reported in a patient with a mixture of CBS and PSP syndrome, whose pathology was CBD.\textsuperscript{72} A patient with MAPT p.G389R presented with progressive aphasia at 38 years of age and later developed CBS. This patient had severe frontotemporal atrophy with Pick body-like inclusions in the cortices and tau-positive threads in the white matter, particularly numerous in the temporal lobe.\textsuperscript{73} A recent study reported five patients with MAPT p.P301T mutation from two pedigrees: the clinical syndrome was CBS in three patients with age of onset in the 40s in two, FTD in one patient, and primary lateral sclerosis in one patient.\textsuperscript{74} All but one CBS patient had autopsies and confirmation of neuropathological features consistent with GGT type II.

**Anti-IgLON5 disease**

Anti-IgLON5 disease is a recently proposed tauopathy characterised by autoantibodies against the neural cell adhesion protein IgLON5 and deposition of both 3R and 4R tau in neurons in a patient with a mixture of CBS and PSP syndrome, whose pathology was CBD.\textsuperscript{72} A patient with MAPT p.G389R presented with progressive aphasia at 38 years of age and later developed CBS. This patient had severe frontotemporal atrophy with Pick body-like inclusions in the cortices and tau-positive threads in the white matter, particularly numerous in the temporal lobe.\textsuperscript{73} A recent study reported five patients with MAPT p.P301T mutation from two pedigrees: the clinical syndrome was CBS in three patients with age of onset in the 40s in two, FTD in one patient, and primary lateral sclerosis in one patient.\textsuperscript{74} All but one CBS patient had autopsies and confirmation of neuropathological features consistent with GGT type II.

**TDP-43 proteinopathy**

TDP-43 is a pathognomonic protein in amyotrophic lateral sclerosis and a subset of FTLD (ie, FTLD-TDP).\textsuperscript{78}–\textsuperscript{79} TDP-43 is a DNA/RNA binding protein located in the nucleus in the physiological state, but forming aggregates of hyper-phosphorylated and ubiquitinated TDP-43 protein in the pathological state. Based on the topographical and cellular distribution of TDP-43 inclusions, FTLD-TDP can be divided into five pathological subtypes.\textsuperscript{80}–\textsuperscript{81} Of those, types A, B and C are frequent. Type A is characterised by numerous neuronal cytoplasmic inclusions and short dystrophic neurites, predominantly in the upper layers of the cortex. The common clinical phenotypes of Type A are bvFTD and progressive non-fluent aphasia. GRN mutations are most often associated with this subtype. Type B is characterised by neuronal cytoplasmic inclusions and sparse dystrophic neurites in all layers in the neocortex. Common clinical phenotypes are bvFTD and motor neuron disease with FTD, and the most common genetic cause is C9orf72 hexanucleotide repeat expansion.\textsuperscript{82}–\textsuperscript{83} Type C is characterised by many long dystrophic neurites and few neuronal cytoplasmic inclusions predominantly in layer 2 of the neocortex, as well as Pick body-like inclusions in the dentate gyrus and neostriatum.\textsuperscript{84} Semantic dementia and bvFTD are common clinical presentations of Type C. No genetic association is known for this subtype.

CBS has been reported as a phenotype of FTLD-TDP.\textsuperscript{11} \textsuperscript{12} \textsuperscript{14} \textsuperscript{85} \textsuperscript{86} In an early study, Maselis et al reported a GRN mutation in familial CBS patients.\textsuperscript{87} This study predicated the discovery of TDP-43 protein as the major constituent of neuronal cytoplasmic inclusions in non-tau FTLD. Benussi et al investigated the frequency of GRN mutations in FTLD and CBS, and found GRN mutations in three of four (75%) familial CBS and one of nine (11%) sporadic CBS patients.\textsuperscript{88} Le Ber et al reported that 3% (1/30) of CBS patients had GRN mutations.\textsuperscript{89} Although these studies lacked pathological assessment, it is reasonable to assume that TDP-43 pathology is the underlying pathology in these patients. Autopsy findings of patients with CBS due to GRN mutations have also been reported. Both p.A9D and p.Serine301CysfsX61 mutations had TDP-43 pathology in the frontal cortex consistent with FTLD-TDP type A.\textsuperscript{90} \textsuperscript{91} A neuroimaging study by Whitwell et al included five sporadic patients with CBS and FTLD-TDP type A; one of them had GRN mutation.\textsuperscript{92} Six patients reported FTLD-TDP due to C9orf72 hexanucleotide repeat expansion is rarely associated with CBS.\textsuperscript{93} To date, GRN mutations are the most common cause of familial CBS.\textsuperscript{94} Of three patients with familial CBS with known genetic mutations in the Mayo Clinic brain bank, two had GRN mutations and one had a PSEN1 mutation.

Sporadic CBS associated with FTLD-TDP type A has also been reported.\textsuperscript{14} In a cohort of 38 patients, 3 of 30 patients with FTLD-TDP type A had CBS, while none of 8 patients with FTLD-TDP type C had CBS.\textsuperscript{85} A study comparing brain atrophy on MRI across patients with CBS, FTLD-TDP showed more significant volume loss in the prefrontal cortex and posterior temporal lobe in the dominant hemisphere than all the other pathologies (ie, AD, CBD and PSP).\textsuperscript{86}

**FUS proteinopathy**

FTLD-FUS is a rare subtype of FTLD compared with both FTLD-TDP and FTLD-tau.\textsuperscript{86} Like TDP-43, FUS exists in the nucleus under the physiological conditions and relocates to the cytoplasm and forms insoluble aggregates under the pathological conditions.\textsuperscript{97} FTLD-FUS can be classified into three clinicopathological subtypes: neuronal intermediate filament inclusion body disease (NIFID), basophilic inclusion body disease (BIBD) and atypical FTLD with ubiquitin-immunoreactive inclusions (aFTLD-U). NIFID is most commonly associated with early-onset bvFTD and less commonly CBS.\textsuperscript{98}–\textsuperscript{99} BIBD is often associated with bvFTD and motor neuron disease,\textsuperscript{100}–\textsuperscript{102} but CBS in patients with BIBD has also been reported.\textsuperscript{102} \textsuperscript{103} A recent study of NIFID and aFTLD-U from the Mayo Clinic brain bank reported that one of seven NIFID and one of eight aFTLD-U patients were clinically diagnosed as CBS.\textsuperscript{16}

**Synucleinopathy**

**Lewy body disease**

LBD is an umbrella term for neurodegenerative disorders characterised by pathological inclusions composed of hyper-phosphorylated a-synuclein in neuronal perikarya in the form of Lewy bodies and in neuronal processes as Lewy neurites.\textsuperscript{104}–\textsuperscript{107} Common clinical presentations are Parkinson’s disease and dementia with Lewy bodies, but LBD can also present with focal cortical syndromes, including CBS.\textsuperscript{108}–\textsuperscript{109} Although pathological findings of a few LBD patients presenting with CBS (LBD-CBS) have been reported,\textsuperscript{110}–\textsuperscript{111} it is difficult to demonstrate a correlation between LBD pathology and CBS because most cases also had a variable degree of AD pathology. A study from Mayo Clinic reported that 11 of 532 (2%) patients with diffuse LBD (DLBD) had clinical presentation of probable CBS (DLBD-CBS).\textsuperscript{112} Of these cases, four patients had a primary pathological diagnosis of PSP, four had a primary pathological diagnosis of AD, and the remaining three patients had DLBD with mild-to-moderate Alzheimer’s type pathology consistent with intermediate likelihood AD; therefore, these concomitant pathologies are the likely pathological correlate of CBS.\textsuperscript{13} In
neuropathological assessments, DLBD-CBS patients had greater atrophy in premotor and motor cortices, as well as corpus callosum than typical DLBD. The number of Lewy bodies and the severity of spongiform changes in the motor cortex were greater in DLBD-CBS than in typical DLBD. These findings indicate that the distribution of pathological lesions is associated with clinical phenotypes, similar to that observed in AD and tauopathies. Recently, Ichinose et al reported a patient with ‘pure’ DLBD who presented as CBS.109 This patient did not have amyloid-β, tau or TDP-43 pathologies; therefore, this case illustrates that the pure LBD can cause CBS.109 Autonomic dysfunction and responsiveness to L-DOPA may help distinguish LBD-CBS from other aetiologies of CBS.109

Multiple system atrophy
MSA is a synucleinopathy characterised by glial cytoplasmic inclusions in oligodendrocytes, composed of hyperphosphorylated α-synuclein, along with neurodegeneration in the striatonigral and olivopontocerebellar systems.110 111 Typical clinical presentations of MSA include variable combinations of autonomic dysfunction, parkinsonism and cerebellar ataxia.112 In a case series of atypical MSA presenting as FTLD, two patients presented as CBS with a disease duration of only 3 years.19 Neither patients had documented autonomic dysfunction that might have suggested clinically probable MSA. In addition to the widespread glial cytoplasmic inclusions with striatonigral degeneration, severe frontotemporal atrophy and abundant α-synuclein-positive neuronal cytoplasmic inclusions, including Pick body-like inclusions, were observed in limbic structures and the neocortex. A caveat of this report is that one of the patients also had moderate Alzheimer’s type pathology, which may have contributed to the CBS clinical presentation. The other patient, however, had only mild medial temporal neurofibrillary tangles without amyloid-β plaques consistent with primary age-related tauopathy,113 which has no known clinical significance. As with cases of LBD, concomitant AD pathology in MSA makes it difficult to demonstrate a causal relationship between MSA pathology and CBS.

Prion disease
There have been multiple reports of CJD presenting with CBS.18 114–116 In the Australian National CJD Registry, 7 of 387 sporadic CJD patients (1.8%) presented as CBS.18 As expected, the disease duration of CJD-CBS was significantly shorter than that of CBD-CBS (5 vs 68 months). Abnormal hyperintensity on diffusion-weighted images, the presence of 14-3-3 protein in cerebrospinal fluid (CSF), and periodic sharp wave complexes on electroencephalogram also suggested CJD. Detection of pathogenic seeding of prions by RT-QuIC using CSF is currently used to diagnose CJD.117 Based on these characteristic clinical and laboratory findings, CJD can be distinguished from other pathologies causing CBS. In rare cases, carriers of mutations in PRNP gene, encoding the prion protein, present as CBS.115 116

Cerebrovascular disease
Cerebrovascular disease can be associated with parkinsonism, and this syndrome is referred to as vascular parkinsonism.114 In rare cases, vascular parkinsonism can mimic atypical parkinsonian disorders, such as PSP or CBS.17 119 Several case reports and autopsy series have described patients with vascular CBS. In most cases, multiple infarcts in the neocortex and basal ganglia are detected with antemortem imaging studies, but a specific pattern of vascular pathology for CBS has not been defined.120–122 Furthermore, most of these studies lack pathological confirmation; thus, the presence of comorbid neurodegenerative changes cannot be excluded. A recent study from the Mayo Clinic brain bank identified 3 of 217 CBS patients with cerebrovascular pathology as a possible correlate of CBS.17 All three patients had small vessel disease in watershed regions, primary motor cortex, deep white matter, thalamus and basal ganglia, as well as secondary corticospinal tract degeneration without evidence of neurodegenerative pathology.

Mixed pathologies
Since ageing is the most important risk factor for neurodegenerative disorders, multiple neuropathological processes, such as AD neuropathological change, argyrophilic grain disease, TDP-43 pathology, Lewy body pathology and cerebrovascular disease occur in elderly individuals.123 124 AD neuropathological change (ie, amyloid plaques, neurofibrillary tangles and neuritic plaques)125 is the most important coexisting neuropathological process in CBS. For example, concurrent AD in PSP may modify clinical presentations, leading to a clinical diagnosis of CBS or dementia, rather than RS.126

Recent advances in molecular biomarkers have greatly improved the accuracy of the clinical diagnosis of AD (see below). It must be noted, however, that a clinical diagnosis of AD does not rule out other disease processes, such as CBD and PSP. A recent study from the Mayo Clinic brain bank reported that 86% of CBD and 89% of PSP had at least minimal AD neuropathological change (ie, Braak neurofibrillary tangle stage ≥0), and 6% of CBD (11/199) and 10% of PSP (97/1020) met the criteria of neuropathological diagnosis of AD (ie, high AD neuropathological change).126 Although a small subset, it should be recognised that high AD neuropathological change can coexist with CBD and PSP, particularly in elderly individuals.

In addition, one should be cautious in drawing correlations between primary pathological diagnoses and clinical presentations. LBD, for instance, almost always has some degree of AD neuropathological change125; therefore, it is difficult to weigh the relative contribution of LBD pathology and AD pathology to the clinical syndrome.13

Fluid and imaging biomarkers for CBS
As discussed above, various neurodegenerative disorders are associated with CBS, but clinical features are not sufficient to predict the underlying pathologies.44 Molecular biomarkers that can detect specific pathological proteins hold promise for improved antemortem diagnoses. Since several reliable biomarkers for AD have been established, a practical approach is first to differentiate AD from other disorders. Representative imaging of AD-CBS and CBD-CBS are provided in figure 5. In this section, CSF and blood biomarkers and PET using tracers for amyloid β, tau and α-synuclein are discussed.

CSF and blood biomarkers
Decreased Aβ42, elevated phosphorylated tau and elevated total tau in CSF have been established as AD-specific patterns, which are useful in the antemortem diagnosis of AD.126 Toledo et al analysed antemortem AD-related CSF biomarkers in 142 autopsy cases, including PSP and CBD and reported that the group with AD pathology could be differentiated from the group without AD pathology with a sensitivity of 96% and specificity of 87%.127 Therefore, the presence of AD pathology in CBS patients can be predicted by measuring AD-associated CSF biomarkers. AD can be ruled out if the biomarker profile is
Figure 5  Representative amyloid PET with [11C]PiB, tau PET with [18F]flortaucipir and glucose PET with [18F]fluoro-2-deoxyglucose (FDG) in AD-CBS and CBD-CBS. The amyloid PET and tau PET are shown on representative axial slices on the same colour scale, while the FDG-PET highlights regional metabolism with z-scores between −1 and −7 SD from controls using CortexID suite software. Upper images are from a patient with AD-CBS. Amyloid PET shows diffuse ligand uptake in cortical grey matter, and tau PET reveals increased signal in the temporoparieto-occipital lobes. FDG-PET reveals hypometabolism in bilateral parietal cortex extending into occipital lobes (right > left) and right > left superior frontal cortex. Lower images are from a patient with CBD-CBS. There is no evidence of increase amyloid PET uptake in the cortical grey matter and there is no increase tau PET uptake. FDG-PET reveals mild hypometabolism in the right premotor cortex and postcentral gyrus in CBD-CBS. AD-CBS, Alzheimer’s disease presenting as corticobasal syndrome; CBD-CBS, corticobasal degeneration presenting as corticobasal syndrome; FDG, fluorodeoxyglucose; L, left; PET, positron emission tomography; PiB, Pittsburgh compound-B; R, right; SUVR, standardised uptake value ratio.

Amyloid PET

Amyloid PET has been developed as an imaging biomarker to visualise amyloid accumulation in vivo. Together with CSF biomarkers, its efficacy in the diagnosis of AD has been established. A meta-analysis of amyloid PET studies reported 23 of 61 (38%) patients with CBS showed amyloid positivity on PET. Interestingly, the frequency of amyloid positivity decreases with age. This finding may be explained by the fact that CBS is strongly associated with hippocampal sparing AD, which usually affects younger individuals compared with other subtypes of AD. AD may contribute to the underlying pathology in young CBS patients, whereas tauopathies and other aetiologies may predominate with increasing age.

As with the interpretation of CSF biomarkers, the possibility of coexisting pathologies other than AD (eg, CBD and PSP) cannot be excluded even in cases where amyloid PET is positive. Therefore, it is not possible to confirm AD as the primary pathology in cases with positive amyloid PET, and it may be necessary to make a diagnosis in combination with other biomarkers such as tau PET. On the other hand, if the amyloid PET is negative, the presence of AD pathology can be ruled out. Other underlying pathologies, especially CBD and PSP, would then be more likely.

Tau PET

Following the success of amyloid PET, tau protein became a target for in vivo molecular diagnosis. Several tau PET tracers have been developed in the last decade. Tau PET may help distinguish tauopathy-CBS from non-tauopathy-CBS and AD-CBS from non-AD tauopathies138 139; however, it remains challenging to differentiate non-AD tauopathies, particularly CBD and PSP.

[18F]flortaucipir, formerly known as [18F]T807 and [18F]AV-1451,140 141 is one of the most widely used tau PET ligands. This tracer has excellent correlation between [18F]flortaucipir retention and distribution of neurofibrillary tangles in AD,142 143 but there have been inconsistent reports on its utility for non-AD tauopathies. One study assessed regional patterns of uptake on [18F]flortaucipir in 14 patients with CBS. Three of six amyloid PET-positive patients showed elevated [18F]flortaucipir uptake across many cortical regions, consistent with AD-CBS. Interestingly, amyloid PET-negative patients who initially presented with apraxia of speech showed increased [18F]flortaucipir retention in the supplementary motor area and precentral cortex; however, patients who had CBS without apraxia of speech did not show significant retention.144 Another study investigated the retention of [18F]flortaucipir in eight patients with CBS; two had bilateral temporal-parietal uptake consistent with AD, and six had retention in the motor cortex and subcortical white matter contralateral to the side of symptoms, presumably due to CBD. Again, the lack of autopsy confirmation is a limitation of this study. PSP-CBS may have similar retention patterns; therefore, the underlying pathology of these six patients remains unclear. In vitro autoradiography using brains from non-AD tauopathies has revealed less binding affinity of [18F]AV-1451 to 4R tauopathies than to AD145 146; therefore, [18F]flortaucipir PET may not reliably detect non-AD tauopathies.147 148

[18F]PI-2620, an analogue of [18F]flortaucipir, has been developed as a second generation tau PET tracer. It has a high affinity for pathological tau aggregates with low off-target binding towards amyloid, monoamine oxidase (MAO)-A and MAO-B.149 [18F]PI-2620 PET could differentiate patients with CBS from cognitively normal individuals without motor symptoms with high sensitivity and specificity. Positive [18F]PI-2620 retention was observed in 91% of amyloid-β-positive CBS and 65% of amyloid-β-negative CBS, while only 7% of control individuals showed positive [18F]PI-2620 retention (93% specificity). The putamen and external segment of the pallidum were the most common regions of retention in the CBS cohort. Cortical retention was highest and most frequent in amyloid-β-positive CBS compared with amyloid-β-negative

not consistent with AD. Even if the CSF biomarkers show AD pattern, interpretation needs to be made with caution; while AD pathology may be present, it does not exclude other pathologies. The presence of phosphorylated tau and total tau in CSF have been investigated as tools to differentiate CBS from Parkinson’s disease and PSP. Both phosphorylated and total tau are elevated in CBS compared with PSP and Parkinson’s disease, but CSF tau has not been shown to differentiate CBS from PSP.130

Neurofilament light chain (NfL) has also been investigated as a potential CSF biomarker for neurodegenerative disorders. NfL is a low molecular weight constituent of neuronal intermediate filaments, and NfL in CSF is considered a marker for axonal damage that lacks disease specificity.131 CSF NfL levels have been reported to be elevated in CBS and PSP clinical syndromes compared with controls, but the levels do not differentiate PSP from CBS.132 Hansson et al used single molecule array, a technology that enables ultrasensitive protein detection in blood, to quantify plasma NfL. Plasma NfL levels were more elevated in MSA, PSP and CBS than Parkinson’s disease or controls, but the levels could not differentiate MSA, PSP and CBS. Another study also reported that serum NfL level was able to accurately distinguish Parkinson’s disease from a combined group of PSP and CBS.134 Taken together, NfL in CSF or blood may be a promising biomarker to differentiate atypical parkinsonian disorders from Parkinson’s disease, but it has not been proven to be useful in distinguishing CBD from PSP.

neurologists currently use these biomarkers. It has not been proven to be useful in distinguishing CBD from PSP.
CBS, with the dorsolateral prefrontal cortex being the most frequent cortical area with retention. This tracer also showed promising characteristics as an imaging agent for PSP in a non-clinical study. Patients with PSP-RS had the highest retention in the internal part of globus pallidus and had a more frequent elevation in the subthalamic nucleus and substantia nigra than controls. A recent study using autopsy-confirmed AD and non-AD tauopathies, however, revealed that [18F]PI-2620 retention was not correlated with tau burden at postmortem pathological assessment.

[18F]PM-PBB3 is another second-generation tau PET tracer, which has great promise to visualise pathological tau aggregates in AD and non-AD tauopathies. The retention of [18F]PM-PBB3 was increased in the primary motor cortex, basal ganglia, brainstem and middle frontal gyri in a patient with CBD confirmed by brain biopsy. In a patient with autopsy-confirmed AD and non-AD tauopathies, [18F]PM-PBB3 retention was increased in the subthalamic nucleus and midbrain. Furthermore, increased retention of [18F]PM-PBB3 was observed in frontal and temporal cortices in a patient with autopsy-confirmed Pick’s disease. Although only one patient from each tauopathy was studied, retention of [18F]PM-PBB3 strongly suggests the possibility of imaging-pathology relationships at a single subject level.

A head-to-head comparison of [18F]PM-PBB3 and [18F]PI-2620 in a patient with PSP-CBS has been reported. Retention of [18F]PM-PBB3 was increased in the midbrain, subthalamic nucleus, thalami, globus pallidus and precentral gyrus, consistent with the expected topographical distribution of tau pathology in PSP. In contrast, retention of [18F]PI-2620 showed a different pattern from that of [18F]PM-PBB3, with increased retention in the globus pallidus and substantia nigra, but weak retention in the thalamus, frontal gyrus and subthalamic nucleus.

THK-5351 PET visualises both tau deposits and MAO-B in vivo. Increased THK-5351 retention was greater in the pre- and post-central gyri and globus pallidus in patients with CBS than in AD and healthy individuals. The THK-5351 retention pattern was different among AD, PSP and CBS, but none of the patients had autopsy confirmation. The underlying pathology of CBS patients remained unclear; therefore, the usefulness of THK-5351 in differentiating the pathology of CBS, particularly CBD or PSP, needs to be elucidated.

**α-Synuclein PET**

PET tracers for α-synuclein are currently under development. Both in vitro and in vivo studies suggest that [11C]PBB3, a first-generation tau PET ligand, has some degree of binding affinity to α-synuclein. C05-01 is the first PBB3 analogue developed as a potential α-synuclein PET tracer. In vitro autoradiography using [3H]C05-01 showed specific binding to α-synuclein in Parkinson’s disease and MSA, but also to amyloid-β and tau pathology. More recently, another PBB3 analogue, C05-05, another promising α-synuclein PET tracer, detected α-synuclein in mouse and monkey models. Although the results of clinical studies in humans have not been reported, this modality will be useful for the early diagnosis of synucleinopathies, which account for a small subset of the underlying pathology of CBS.

**CONCLUSIONS**

CBS is a clinical syndrome caused by various underlying pathologies, with the most frequent pathologies at autopsy being CBD and PSP. At present, pathological assessment is required for definitive diagnosis, but in the future, it may be possible to predict the underlying pathology during life based on a combination of clinical symptoms and signs with supporting information from various biomarkers. Biomarker research is most reliable when it is based on neuropathologically confirmed cases. Accumulation of autopsy-confirmed cases is time-consuming, but extremely important. Clarification of the abnormal proteins that cause the disease is expected to lead to the development of disease-modifying therapies that target those proteins for treatment. For this purpose, it is necessary to conduct prospective cohort studies with pathological diagnosis to gather knowledge on the correlations between clinical symptoms or signs, biomarkers and pathological diagnosis.

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SK searched the literature, prepared tables and figures, and wrote the first draft. KAJ, MY and DWD reviewed and edited the manuscript. All authors drafted and approved the final manuscript.

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