ÖSSZEFOGLALÓ KÖZLEMÉNY

REVIEW ARTICLE

Corticobasal degeneration: An update

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Corticobasal degeneration (CBD) is one of the primary tauopathies with a disease onset in the 5th to 7th decade. CBD is a progressive condition of unknown aetiology, which is characterised neuropathologically by neuronal loss, astrogliosis and deposition of filamentous tau inclusions, composed entirely of 4-repeat tau isoforms, in neurons and glial cells in cerebral cortical areas, basal ganglia, brainstem and cerebellar nuclei. The term CBD is now a neuropathological diagnostic one and for the canonical clinical syndrome associated with CBD neuropathological changes, the corticobasal syndrome (CBS) term is used. In addition to CBS, the clinical spectrum also includes a behavioural variant of frontotemporal dementia syndrome, speech disorders, Richardson's syndrome and, rarely, posterior cortical syndrome. In addition to CBD, CBS can also be caused by other pathologies. A number of genetic risk factors of CBD have been identified. As specific biomarkers confirming CBD as the underlying pathology responsible for CBS or other clinical manifestations are still lacking, for a definitive diagnosis of CBD neuropathological investigation is required. Recent cryo-electron microscopic studies have proven that CBD is a distinct tauopathy associated with a unique molecular structure of the tau filaments, which firmly differentiates it from other primary tauopathies.

Keywords: corticobasal degeneration, corticobasal syndrome, tauopathy

A corticobasalis degeneráció korszerű szemlélete

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A corticobasalis degeneráció (corticobasal degeneration, CBD) egy olyan ritka, ismeretlen etiológiájú progresszív neurodegeneratív betegség, ami általában 50–70 éves kor körül kezdődik. A CBD a primer taupathiák egyik típusa, amit neuropatológiailag idegsejtpusztulás, astrogliosis, valamint az idegsejtekben és a gliasejtekben megtalálható, tau fehérjéből felépülő inclusiók jellemzik. A CBD-ben a tau inclusiók jellegzetesen, kizárólag úgynevezett négy microtubuluskötő régiót tartalmazó tau izoformákat tartalmaznak. A tau patológia agyi corticalis régiókat, basalis ganglion struktúrákat, agytörzsi és cerebellaris magvakat érint. A CBD diagnózis kizárólagosan neuropatológiai, a klasszikus klinikai tünetegyüttesre a corticobasalis szindróma (corticobasal syndrome, CBS) elnevezést használják. A CBD-re specifikus neuropatológiai elváltozások a CBS mellett más klinikai tünetegyütteseket is okozhatnak, így frontotemporalis dementiát, beszédzavarokat, Richardson-szindrómát és ritkán úgynevezett posterior corticalis szindrómát. Megjegyzendő az is, hogy CBD-n kívül egyéb típusú patológia is állhat a CBS hátterében. Számos genetikai rizikófaktor vált ismertté CBD-ben. Betegségspecifikus biomarkerek hiányában a CBD diagnózis megállapításához neuropatológiai vizsgálat szükséges. A közelmúlt krio-elektronmikroszkópos vizsgálatai igazolták, hogy a CBD-ben szenvedett betegek agyából izolált tau filamentumok molekuláris struktúrája egyedi, ami egyértelműen elkülöníti a CBD-t más taupathiáktól.

Kulcsszavak: corticobasalis degeneráció, corticobasalis szindróma, taupathia

A majority of the neurodegenerative diseases affecting the central nervous system share the common feature that they are characterised by an age-dependent misfolding of specific disease-proteins, which self-assemble into β-sheet rich oligomers and finally into highly insoluble intracellular or extracellular fibrils of amyloid nature[1]. The ultimate consequence of this process is believed to be nerve cell death with progressive loss of cerebral function, manifesting in a number of clinical syndromes, such as dementias, movement disorders, ataxias, and motor neuron diseases. The proteins that are commonly involved in neurodegeneration include the Alzheimer's amyloid-β peptide, the microtubule-associated protein tau, α-synuclein, the TAR DNA-binding protein-43kDa (TDP43) and huntingtin. In a large group of neurodegenerative diseases, known as tauopathies, the abnormally hyperphosphorylated tau protein forms filamentous inclusions in nerve cells and, in some diseases, also in glial cells. One such tauopathy is corticobasal degeneration (CBD), which is the focus of this review.

CBD was first described as a distinct clinicopathological entity by *Rebeiz* et al. from the Massachusetts General Hospital, Boston as 'corticodentatonigral degeneration with neuronal achromasia,' first in an abstract in 1967[2], and then in a full-length paper in 1968[3], although it is possible that cases reported earlier such as the one published by *Jean Lhermitte* and colleagues in 1925, may represent the same entity[4]. The now widely used term CBD was introduced by *Gibb* and colleagues, from the National Hospital for Neurology and Neurosurgery and King's College Hospital, both in London, UK two decades later. They described a characteristic clinical syndrome, for which the term corticobasal syndrome (CBS) is used today[5], and the results of their neuropathological investigations[6]. The term corticobasal ganglionic degeneration was subsequently also recommended, but this has never caught on[7].

CBD, affecting both sexes equally, is a rare progressive, currently untreatable neurodegenerative disorder of unknown cause. It is a sporadic condition, associated with genetic risk factors (see below). Disease onset typically is in the 5th to 7th decades of life; the average disease duration is about 7 years[5], although autopsy-confirmed cases with a disease duration of 3 years or less, designated as 'rapidly progressive CBD', have been described (see also below)[8]. The data that is available about the epidemiology of CBD, is scanty. The estimated prevalence of CBD varies between 4.9-7.3 cases per 100 000 individuals while its estimated incidence rate is 0.02 cases per 100 000 individuals[9]. Most prevalence studies have relied on clinically defined CBS, rather than pathologically confirmed CBD. Given that CBD pathological changes can cause several different clinical syndromes (see below), and that there is no reliable biomarker, the underlying prevalence of pathologically defined CBD is difficult to determine.

Although originally CBD presenting clinically as CBS was described as a movement disorder, subsequent studies clearly demonstrated that the clinical presentation could vary and present like progressive supranuclear palsy (PSP), Richardson syndrome-like picture (CBD-RS) and disorders of cognition (see below). CBD is therefore, now classified both as an atypical Parkinsonian disorder[10, 11], and as a frontotemporal lobar degeneration with tau-positive inclusions (FTLD-tau)[12].

In addition to the recognition of the wide spectrum of clinical phenotypes with underlying CBD neuropathological changes, a number of other pathologies such as PSP, Alzheimer's disease (AD), FTLD with TDP43-positive inclusions (FTLD-TDP), Pick's disease, which is classified as a subtype of FTLD-tau, globular glial tauopathy type II (GGT II), Creutzfeldt-Jakob disease, FTLD with fused in sarcoma protein inclusions (FTLD-FUS) and MSA can be associated with CBS[13–20]. Furthermore, familial cases with a CBS clinical phenotype and FTLD-TDP pathology, due to a mutation in the progranulin (*GRN*) or the *C9orf72* gene, have also been documented[21–25]. In particular, an association between the IVS6-1G>A mutation in *GRN* gene and a CBS clinical phenotype was reported[22]. Such a discrepancy between clinical phenotype and the underlying pathology, together with lack of specific molecular and imaging biomarkers explain the relatively low accuracy of the antemortem prediction of CBD neuropathological changes (see also below)[5, 15, 26, 27]. As a consequence, neuropathological examination is required in order to make a definitive diagnosis of CBD.

Clinical syndromes with underlying CBD pathology

CBD neuropathological changes, for which the term CBD is now exclusively used, may cause distinct clinical pictures linked approximately to the anatomy of the predominant pathology[5, 20, 26, 28–30]. These syndromes may overlap, and as the disease progresses the predominant phenotype may change. The prototypic phenotype is CBS in cases with underlying CBD neuropathological changes[31, 32]. In CBS there is progressive, asymmetric ideomotor apraxia with myoclonus, rigidity, parkinsonism and dystonia[5], which reflect involvement of the parieto-frontal cortex, basal ganglia and substantia nigra[6, 33]. There may be accompanying cortical sensory loss due to parietal lobe involvement. CBS is not uncommonly initially misdiagnosed as Parkinson's disease or as a stroke. The most important clinical clues which lead to a diagnosis of CBS are lack of response to levodopa, the presence of marked ideomotor apraxia and rapid deterioration. CBS

may itself be caused by different underlying pathologies including PSP, AD and FTLD-TDP43 pathology (see also above). The frequency of underlying pathology in a CBS cohort is likely to vary according to the clinical referral setting with AD pathology being more common in referral of CBS cases to cognitive disorders clinics. Estimates of the frequency of underlying CBD pathology in studies comprising around 100 patients with CBS vary between 24% and 38%[19, 26]. The diverse pathology of CBS and the current lack of a reliable biomarker for underlying pathology in life limits our ability to develop disease modifying treatment trials.

Patients with CBD underlying neuropathology developing progressive frontal/dysexecutive syndromes with frontal lobe atrophy have variously been described as having frontal lobe dementia or frontotemporal dementia (FTD) and this is now most commonly described as behavioural variant FTD (bvFTD). Recent case series have reported that 6-9% of clinically defined bvFTD cases have underlying CBD pathology[28, 34]. These case series are small and around half will develop an overlapping motor and cognitive syndrome with apraxia/parkinsonism and bvFTD and around 50% will have a pure bvFTD syndrome. CBD can also cause progressive non-fluent aphasia (PNFA) and apraxia of speech (AOS). In PNFA, there is usually progressive loss of speech output with short sentences, agrammatism and phonemic errors, in contrast to the difficulties with naming, loss of semantic function and preserved grammar in semantic dementia. In AOS there may be dysarthria, effortful speech output and word distortions and misarticulation. A recent case series identified CBD as the commonest cause of PNFA, underlying 39% of PNFA cases at autopsy[35]. CBD has also been identified as a common cause of AOS and CBD accounted for 45% of PNFA/AOS overlap syndrome cases[35].

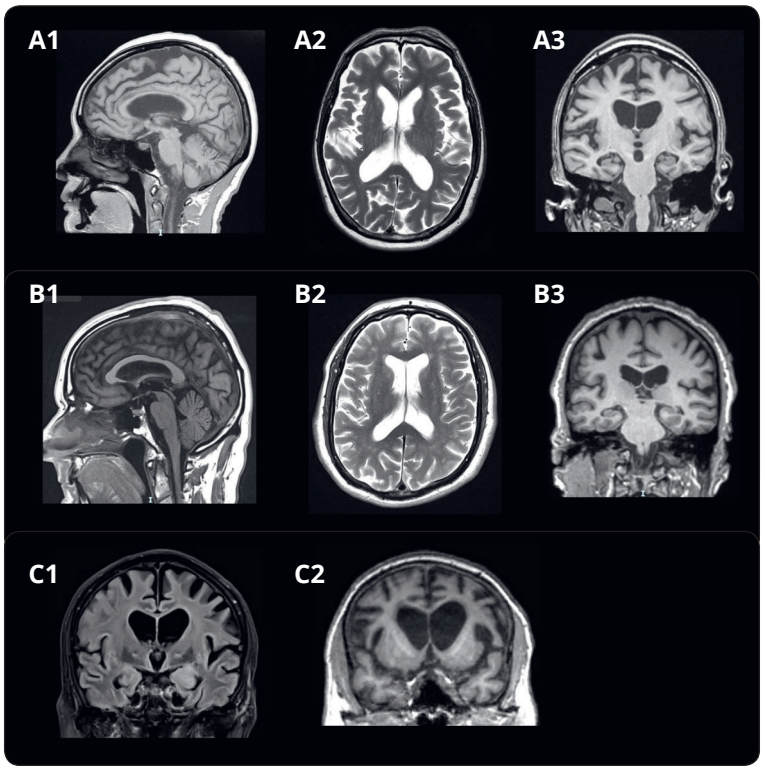

Figure 1. *Magnetic resonance imaging in CBD-CBS, CBD-PNFA and CBD-bvFTD cases.* **A:** *MRI images of a patient with CBD-CBS (A1 = T1 sagittal, A2 = T2 axial, A3 = T1 coronal), showing marked cortical atrophy, especially within the posterior frontal and parietal regions. The middle part of corpus callosum shows thinning and there is asymmetric parietal atrophy. The hippocampi are relatively preserved.* **B:** *MRI images of an age-matched control (B1 = T1 sagittal, B2 = T2 axial, B3 = T1 coronal) showing mild cortical atrophy in keeping with age.* **C:** *MRI images showing an asymmetrical, left more than right frontal atrophy in a partient with PNFA (C1 = FLAIR coronal) and bifrontal atrophy in a patient with bvFTD (C2 = T1 coronal). In both cases the the diagnosis of CBD was confirmed neuropathologically. (Images C1 and C2 are courtesy of professor Jonathan Rohrer, Dementia Research Centre, Institute of Neurology, Queen Square, London; bvFTD – frontotemporal dementia, behavioural variant; CBD = corticobasal degeneration; CBS = corticobasal syndrome; PNFA = progressive non-fluent aphasia)*

Based on brain bank series clinical diagnostic criteria have been developed by *Armstrong* and colleagues which have been widely used in defining CBS and also include criteria for clinically probable and possible CBD. Importantly, the listed exclusion criteria include clinical features suggestive of MSA and DLB, and biomarker evidence of AD, which help to exclude CBD-mimics. They also include definition of the major clinical syndromes associated with CBD pathology – CBS, fronto-behavioural syndromes (FBS), PSP syndrome (PSPS) and the nonfluent agrammatic variant of primary progressive aphasia (NAV)[5].

Imaging

Typically, CBS involves asymmetric posterior frontal and superior parietal atrophy with progressive loss of cortical volume and subcortical white matter and middle corpus callosum atrophy in serial imaging **(Figure 1)**, although some studies have indicated that such MRI changes alone

do not differentiate groups of CBS cases with or without underlying CBD pathology[36]. In a recent large study of 113 patients with CBS and neuropathological follow-up, *Shir* and colleagues compared the neuroimaging features of patients with different underlying pathologies, CBD, PSP and AD, which were responsible for 80% of the cases with a CBS clinical presentation[19]. Patients with CBD or PSP pathology had the most significant volume loss in premotor areas with subcortical white matter volume loss, as compared to patients with CBS and underlying AD pathology, in which widespread cortical grey matter loss was characteristic[19]. A large study of 135 clinically diagnosed patients, applied a machine learning based sequential volumetric analysis to model both the heterogeneity and progression of volume loss in patients with CBS and volumetric brain imaging ordered by progressively increasing regional atrophy (Subtype and Stage Inference – SuStain)[37]. In keeping with the findings of Shir and colleagues[19], the data could be clustered into either two or three groups with the group with the highest proportion of underlying CBD pathology being characterised by a pattern of atrophy which starts in the posterior frontal cortex and basal ganglia, then affects the insula and parietal regions with the most extensive regional involvement including atrophy of the midbrain, thalamus parietal and occipital cortices[37].

Biomarkers

There are no well-established biomarkers for CBD pathology in life, however both amyloid-PET (positron emission tomography) and cerebrospinal fluid (CSF) and blood biomarkers can be of significant help. Changes indicative of extensive cerebral amyloid deposition on amyloid PET imaging or reduced CSF amyloid-β levels together with elevated p-tau 217 (tau phosphorylated at threonine 217) and p-tau 181 (tau phosphorylated at threonine 181) levels in CSF or plasma[38] can signal underlying AD pathology. Such findings increase the likelihood of primary AD pathology as the underlying cause of CBS[39]. It should be noted, however that AD co-pathology is not uncommon in CBD and PSP and so positive blood or CSF biomarkers may indicate underlying AD co-pathology rather than confirming that CBS is due to AD. CSF and plasma neurofilament-light chain protein (NFL) is elevated in CBD/CBS patients in comparison to patients with AD or Parkinson's disease but this is a non-specific marker of CBD as NFL is also elevated in PSP, other FTLD conditions and amyotrophic lateral sclerosis. Tau seeding assays using the biological tissue to trigger the aggregation of 4-repeat tau (4R-tau) (rtQUIC or PMCA) have shown promise in that they can efficiently distinguish CBD and PSP using material from brain tissue[40], but to date these assays have not worked reliably or found reproducible in CSF or with other biomaterials from living patients. In the future, we anticipate that the combination of fluid and imaging biomarkers will help to predict underlying CBD pathology with a high degree of accuracy paving the way for specific therapeutic trials.

Genetics

There is a substantial overlap between the genetics of PSP and CBD. Both sporadic PSP and CBD are associated in European individuals with the common 17q21/*MAPT* H1 inversion haplotype[41]. As both PSP and CBD are 4R-tauopathies, this suggests that the association between these sporadic 4R-tauopathies and the H1 inversion may relate to the alternative splicing mechanism of the tau gene (see also below). There has been one relatively small genome wide association study (GWAS) of CBD comprising 219 cases and 3768 controls. This confirmed the genetic overlap between PSP and CBD with an association between CBD and the *MAPT* H1 haplotype, a *MAPT* H1 sub-haplotype defined by the *MAPT* promoter single nucleotide variants rs242557 and variation at the *MOBP* locus, encoding the myelin associated oligodendrocyte basic protein. This study also identified a novel association between at a SNV close to the KIF-13B1 locus and CBD[42]. Given the relative paucity of pathologically confirmed CBD cases further advances in the genetics of sporadic CBD are likely to entail including clinically diagnosed cases with imaging or fluid biomarker support for an underlying CBD diagnosis.

The cases reported as familial most likely represent variants of 'frontotemporal dementia with parkinsonism linked to chromosome 17 *MAPT'* (FTDP17 *MAPT*) with overlapping clinical and pathological features[43]. Accordingly, a series of such cases have been described as having characteristic CBD pathology. Recently the *MAPT* mutation L284R, previously described as causing familial PSP was identified in a patient with typical CBD pathology at autopsy[44]. Other *MAPT* mutations described as causing CBD pathology include S305S, *MAPT* exon 10 + 16 intronic mutation, R406W and N410H mutations[45]. Some of these mutations, for example *MAPT* exon 10 + 16 may be associated with overlap pathology with features of both PSP and CBD. Recently, intermediate (non-pathogenic) repeat expansions in the *C9orf72* gene have been reported to be associated with CBD but this finding needs to be replicated in larger case series[46].

Neuropathology of CBD

Examination of brains with CBD, reported in the first publications, confirmed cortical atrophy with nerve cell loss in the superficial cortical layers, the presence of swollen achromatic neurons or Pick cells in the affected cortices and involvement of subcortical and brainstem structures[3, 6]. It is of note that the initial studies, using traditional

silver impregnation techniques, such as the *Bielschowsky*'s method, but not the *Gallyas* method, failed to identify neurofibrillary tangles, except in the substantia nigra, for which the now redundant term 'corticobasal inclusions' was recommended[6].

Macroscopic findings

Macroscopic investigation of larger cohort of CBD cases demonstrates that the cortical atrophy preferentially affects the superior posterior frontal and parietal regions including the precentral and postcentral gyri and, in cases with CBS, relative sparing of the temporal and occipital regions[47]. It is of note that in CBS cases the atrophy is often asymmetrical and the more severe changes are seen contralateral to the clinically most severely affected limbs **(Figure 2A)**[48]. The cortical atrophy is more apparent in the frontal and temporal lobes in cases with FTD or PNFA[47, 49–51]. There is variable dilatation of the ventricular system, the cerebral white matter may be reduced, and the corpus callosum usually shows thinning. Flattening of the caudate nucleus **(Figure 2B)** and discolouration of the globus pallidus may be seen while atrophy of the subthalamic nucleus, which is typically a prominent feature of PSP, is absent. In clinically end-stage cases, which represent the majority of neuropathologically examined cases[52], pallor of the substantia nigra may be marked **(Figure 2C)** while the pigmentation is usually better preserved in the locus coeruleus **(Figure 2D)**. It is of note that in cases when death occurs relatively early in the disease course due to a second illness, the substantia nigra may be better pigmented (see also below)[8].

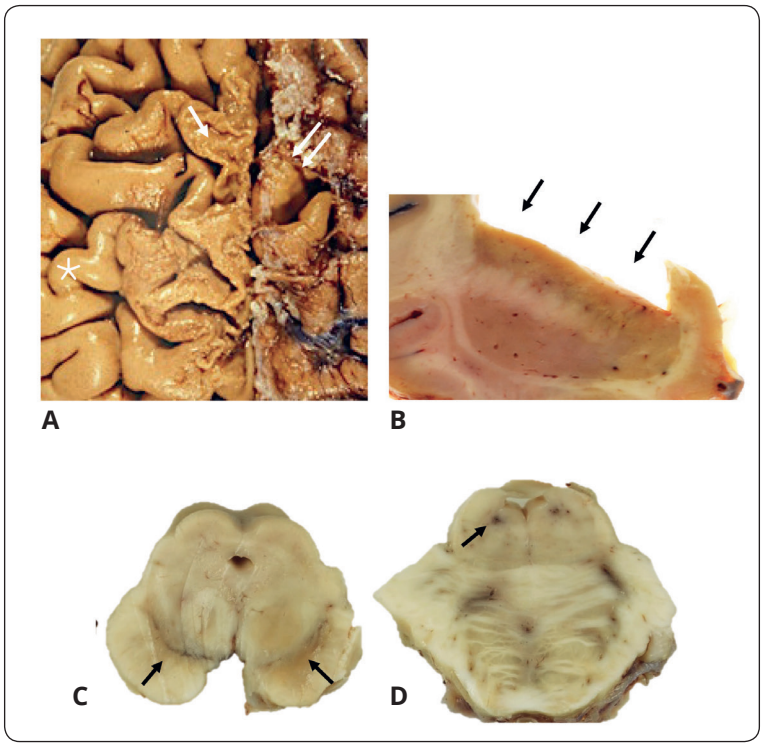

Figure 2. *Representative macroscopic abnormalities in CBD.* **A:** *As in this case with corticobasal syndrome clinical presentation, the cerebral cortical atrophy may be severe, 'knife-edge' type in the superior frontal gyrus on one side (single arrow) while the same gyrus on the other side is better preserved (double arrow). The parasagittal distribution of the cortical atrophy is emphasised by the less affected middle frontal gyrus on the side of the severe cortical atrophy (asterisk). The asymmetry of the cerebral cortical atrophy is common in CBD.* **B:** *The caudate nucleus often has a flattened ventricular surface (triple arrow).* **C:** *In advanced cases the substantia nigra shows marked pallor (single arrows) while the locus coeruleus in the pons (***D***) is better pigmented (arrow). (CBD = corticobasal degeneration)*

Microscopic findings

Microscopic investigation reveals neuronal loss with astrocytosis and microvacuolation of the neuropil **(Figure 3A)** in the superficial cerebral cortical layers in affected cerebral areas. Although swollen achromatic neurons (Pick cells), possessing enlarged, often vacuolated cytoplasm lacking Nissl substance and eccentrically placed nuclei, are common (**Figure 3A**, insert), their presence is not required for the neuropathological diagnosis of CBD[50]. Neuronal loss, astrocytosis and occasional ballooned neurons are variable in subcortical grey nuclei such as the globus pallidus.

Severe loss of neurons in the substantia nigra is a feature of clinically 'end-stage' CBD cases where both the dopaminergic neurons of the pars compacta, identifiable by their neuromelanin pigment, and the non-pigmented GABAergic neurons of the pars reticulata are severely affected[53]. This pattern of nigral nerve cell loss is also a feature of PSP[53, 54], but not of Parkinson's disease where the dopaminergic neurons of the pars compacta are selectively lost[55]. While nigral neuronal loss is considered a hallmark pathological feature of CBD, neuropathological studies have demonstrated that nigral neuronal loss is not an early feature of the pathological process. Our own studies have shown that this is entirely absent or only mild in cases with preclinical or incipient disease and, compared with 'end-stage' cases, it is significantly less severe in cases where, due to a second illness, death occurs early[8, 52]. This observation is also supported by

dopamine transporter (DAT)-single photon emission tomography (SPECT) studies of cases, in which, after death, the diagnosis of CBD was confirmed pathologically. In such cases baseline scans, carried out relatively soon after clinical disease onset, showed only mild abnormalities while follow-up scans, performed years later, confirmed the presence of severe decline of striatal DAT binding[56].

The pons, medulla, cerebellum and spinal cord are microscopically normal when assessed on tissue sections stained with haematoxylin and eosin stain, but in the 'CBD with olivopontocerebellar atrophy (CBD-OPCA) and TDP43 pathology' variant these structures show considerable neuronal cell loss (see also below)[57]. The corticospinal tracts may show evidence of degeneration[58]. The spinal cord is also unremarkable when assessed on haematoxylin and eosin-stained sections.

Using tau immunohistochemistry with antibodies specific to phospho-tau, such as the widely used AT8 antibody recognising pSer202/pThre205 residues reveals the complexity of the tau pathology in CBD **(Figures 3** and **4)**. Such studies demonstrate a gradual increase in the cortical tau load towards the posterior frontal and parietal cortices **(Figure 4)**. The tau pathology includes numerous neuronal inclusions, including neurofibrillary tangles and pretangles **(Figure 2E, F)**. As opposed to neurofibrillary tangles, pretangles do not have a filamentous internal structure, but show a diffuse, granular staining pattern[47, 59]. The tau-positive neuronal inclusions are particularly prominent in areas of superficial microvacuolation in moderately affected cerebral cortices, but are present also in subcortical grey nuclei, hippocampus, amygdala, substantia nigra, other brainstem nuclei, cerebellar dentate nucleus and also in spinal cord neurons[47, 50, 59–61]. Tau-positive coiled bodies, representing filamentous oligodendroglial cytoplasmic inclusions, are seen in both grey structures and white matter **(Figure 2D)**[60, 62]. The characteristic lesions, the presence of which is required for the neuropathological diagnosis of CBD, are the *astrocytic plaques*, which can be demonstrated by tau immunohistochemistry and the Gallyas silver impregnation technique. The astrocytic plaques are composed of short, stubby processes forming distinct annular structures surrounding a cell-free zone of neuropil, which may contain an astrocytic nucleus **(Figure 2E, G)**[59, 63]. The characteristic morphology is due to accumulation of hyperphosphorylated tau in distal astrocytic processes[62, 64, 65], which is in contrast with the pattern of tau deposition in *tufted astrocytes*, which are pathological hallmark lesions in PSP. In this latter, accumulation of tau into the cell body and the proximal astrocytic processes gives rise to an entirely different morphology **(Figure 2H)**[47, 59]. Astrocytic plaques have been described to show an association with cerebral vasculature[66], the significance of which will be discussed below. The astrocytic plaques are most abundant in the premotor and prefrontal cortical regions and also in the caudate nucleus[67]. Tau-positive neuropil threads are characteristically numerous in both grey and white matter structures of the cerebrum **(Figure 2B, C, F)**, brainstem and cerebellum. They are particularly abundant in the white matter underlying affected cerebral cortices **(Figure 2B)**[10, 26].

Application of differential tau immunohistochemistry with antibodies specific to either 4R-tau or 3R-tau, confirm that all types of tau-positive lesions are exclusively labelled with the antibody specific to 4R-tau isoforms[59, 68].

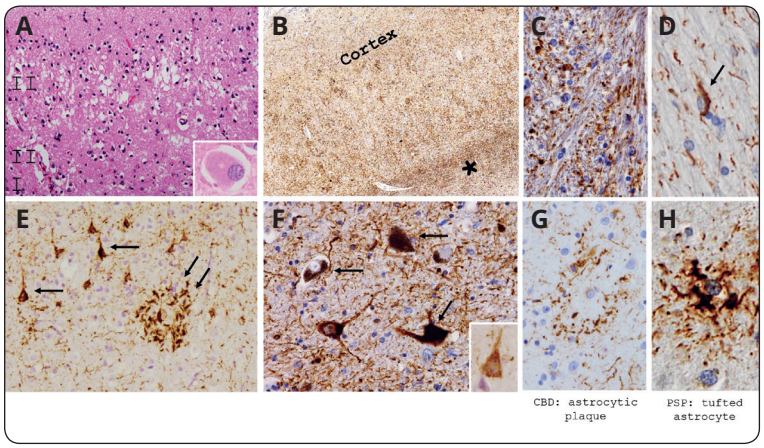

Figure 3. *Light microscopic findings in CBD.* **A:** *Nerve cell loss and marked neuropil microvacuolation is present in layers II and III in the frontal cortex, the insert showing a ballooned cortical neuron with enlarged, vacuolated cytoplasm lacking Nissl granules.* **B:** *Tau immunohistochemistry demonstrates abundant tau deposition in both cerebral cortex and subcortical white matter (*).* **C:** *Tau-positive neuropil threads are also numerous in the subcorical and deep hemispheric white matter where* **D:** *oligodendroglial coiled bodies are present (arrow).* **E** *and* **F:** *Neurofibrillary tangles (examples highlighted by single arrows) and pretangles (insert on* **F***) from the frontal cortex. A large astrocytic plaque is also present on panel E (double arrow).* **G:** *The photomicrograph shows an astrocytic plaque comprising a peripheral rim of tau-positive processes surrounding a clear zone of neuropil in which an astrocytic nucleus is seen.* **H:** *For comparison, the panel shows tau deposition in the cytoplasm and proximal processes of a tufted astrocyte, which is the hallmark lesion in progressive supranuclear palsy. (***A:** *haematoxylin and eosin staining,* **B – H:** *phospho-Tau immunohistochemistry, AT8 phospho-tau antibody; CBD = corticobasal degeneration)*

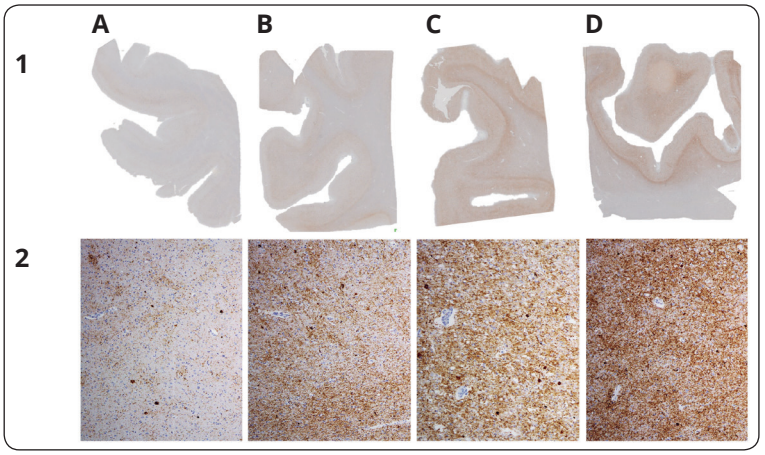

Figure 4. *Tau pathology in different cortical regions in a case with of CBD-CBS. The photomicrographs taken with very low (row 1) and moderate magnification (row 2) demonstrate a gradual increase in the severity of tau deposition in the different cortical areas. This is the mildest in the temporal cortex (***A***), intermediate in severity in the prefrontal cortex (***B***) and the most severe in the posterior frontal (***C***) and parietal (***D***) cortices. (CBD-CBS: corticobasal degeneration with corticobasal syndrome;* **A – D:** *phospho-Tau immunohistochemistry, AT8 antibody)*

Neuropathological diagnostic criteria have been established for CBD, which require the presence of the above-described tau inclusions in both neurons and glia. The presence of astrocytic plaques and extensive thread pathology are of differential diagnostic significance[50].

CBD clinicopathological subtypes and common co-pathologies

There are a number of clinicopathological CBD subtypes in which differences in the distribution and severity of the underlying neuronal loss and tau pathology are seen. Importantly in all subtypes, the characteristic microscopic tau lesions and the biochemical characteristics of the disease-associated tau are identical (see also below)[69]. In the classical clinical subtype, CBD-CBS the tau pathology is greater in the primary motor cortex, somatosensory cortices and the putamen while cases with a Richardson's syndrome clinical presentation, which is a common variant (CBD-RS), have a greater tau burden in limbic and hindbrain structures[69]. As already described above, in some cases with CBD underlying pathology, the clinical presentation may be dominated by cognitive features, including bvFTD or speech disturbances[26, 70–73]. One clinicopathological study from the large Mayo Clinic Brain Bank in Jacksonville, Florida demonstrated that in cases with cognitive predominant features, the CBD-type tau pathology was more severe in the temporal and less severe in the peri-Rolandic cortices than in CBD-CBS while argyrophilic grain disease (AGD), which is a common second pathology in CBD (see also below) occurred more frequently than in cases with a typical CBS presentation[71]. In the rare CBD-OPCA variant, in comparison with CBD-CBS cases, there is marked neuronal loss in pontine nuclei, inferior olivary nucleus, cerebellar dentate nucleus and Purkinje cell layer[57]. In such cases the tau-burden is greater in infratentorial structures, in particular in the pontine base than in typical CBD[57]. In cases with posterior cortical atrophy syndrome, the involvement of the occipital lobe may be prominent[47].

Rarely characteristic neuropathological findings of CBD can be observed in clinically asymptomatic cases, designated 'preclinical CBD'[52]. Our study of such cases indicated that the overall tau-burden in typical, end-stage CBD is several times greater than in 'preclinical CBD', in which lesions such as cortical microvacuolation, ballooned neurons and nigral cell loss were absent or only minimal. Another consistent feature of the preclinical cases was a predominance of astrocytic plaques over neuronal tau pathology (see also below)[52].

Although CBD, after an insidious onset typically shows a slowly deteriorating disease course with a seven-year mean survival[32], cases with a disease duration of three years or less have been rarely also documented[8, 74–76]. In the large CBD post-mortem cohort (N=124), which became available for our studies, we identified 6 cases (5% of the entire cohort), designated as fulminant or 'rapidly progressive CBD'. In this CBD variant, despite the significantly short disease duration, the neuropathological changes, including the overall tau-burden and nigral cell loss are advanced **(Figure 5)**. The prominence of neuronal tau lesions over astrocytic plaque pathology was also a feature, which indicates that cellular vulnerability in this CBD variants deviates from that seen in other subtypes[8]. One of the clinical implications of rapidly progressive variants of neurodegenerative diseases such as CBD, AD and also other neurodegenerative diseases[8, 74, 77] is that their skewed representation in therapeutic trials potentially may result in misinterpretation of treatment outcomes[77].

TDP43 co-pathology in CBD

Co-existence of TDP43 pathology is a common finding in CBD and, irrespective of disease subtype, its frequency has been found to vary between 33% and 45% in the different studies[78, 79]. TDP43-positive neuronal and glial cytoplasmic inclusions and also threads are wide-

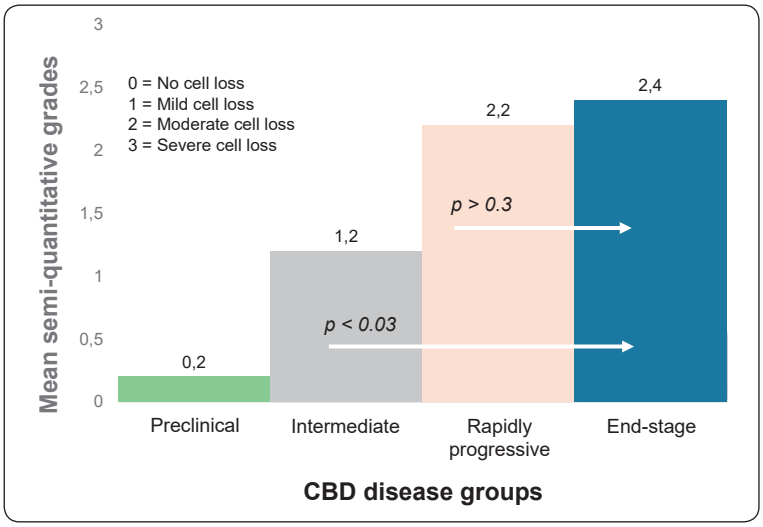

Figure 5. *Nigral cell loss in four subgroups of CBD. The figure demonstrates that the severity of nigral neuronal loss is closely associated with disease progression in CBD as it is minimal (or absent) in preclinical cases and is statistically significantly milder in the intermediate cases, death occurring prematurely due to a second illness, than in end-stage disease. Despite the short disease duration, in the rapidly progressive group the degree of nigral cell loss is similar to that is seen in end-stage CBD. (Figure modified after Figure 3 in Ling et al. Acta Neuropathol 139:717-734, 2020; CBD: corticobasal degeneration)*

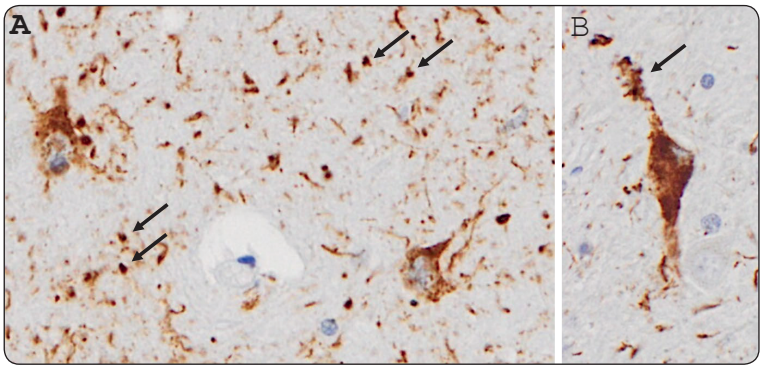

Figure 6. *Tau (argyrophilic) grain pathology is common in CBD.* **A:** *Tau-positive grains (arrows) are numerous in the CA1 hippocampal subregion of a case with CBD where neurons with dystrophic dendritic degeneration (***B****) were also present in CA4 neurons (arrow). (CBD: corticobasal degeneeration;* **A** *and* **B:** *phospho-Tau immunohistochemistry, AT8 antibody)*

spread in the basal ganglia and also olivopontocerebellar structures in the CBD-OPCA variant[57]. A comprehensive study from the Mayo Clinic Brain Bank, which investigated 187 CBD cases, found that cases with severe TDP43 pathology are more likely to have been diagnosed *in vivo* as PSP compared with those in which the TDP43 pathology was limited or entirely absent[79]. Another interesting finding of this study was that the *MAPT* H1/H1 genotype frequency was significantly lower in cases with severe TDP43 pathology than in cases in which the TDP43 pathology was limited or absent[79]. The presence of TDP43 inclusions in cholinergic spinal cord motor neurons and in primary motor cortex was recently demonstrated in about 60% of otherwise typical CBD cases[80].

Argyrophilic (tau-positive) grains in CBD

Argyrophilic grain disease (AGD) is a distinct neuropathological entity, commonly found in elderly individuals and can be rarely the pathology underlying FTD[81]. The hallmark lesions of AGD are the comma or spindle-shaped *grains*, which represent accumulation of hyperphosphorylated 4R-tau in dendrites, dendritic side branches and axons, occurring most commonly in medial temporal lobe structures[82]. In addition to grains, pretangles, neurofibrillary tangles, oligodendroglial coiled bodies, distinct granular/fuzzy astrocytic inclusions and dendritic dystrophy of neurons of the CA4 hippocampal subregion are also present **(Figure 6)**[83]. It is of note that tau-positive, argyrophilic grains occur as a second pathology of uncertain clinical significance, in association with a number of neurodegenerative diseases, including CBD. The frequency of argyrophilic grains is significantly higher in CBD than in dementia controls and found in at least 40% of the cases[84, 85].

The tau protein and neurodegeneration

The natively unfolded, microtubule-associated protein tau is mainly an axonal protein with dendritic spines (post-synapse), neuronal soma and axonal presynaptic terminals being additional sites [86]. Tau protein mRNA is also expressed at low levels by glial cells[87–89]. Tau promotes formation and stabilisation of microtubules, which is a precondition of cytoskeletal organisation and trafficking. These latter are important for preserving the viability of neurons, which are dependent on maintaining a bidirectional transport of cellular cargoes in axons and dendrites[90]. The single human tau (*MAPT*) gene is located on chromosome 17q21 and possesses a noncoding exon 0 and 14 coding or partially coding exons[91]. Alternative splicing of exons 2, 3

and 10 results in the expression of six tau isoforms in adult human brain[92], which are defined by the presence or absence of 29 or 58-amino-acid-long N-terminal inserts and whether they contain a fourth 31-amino-acid-long repeat in their microtubule-binding domain. Of the six tau isoforms, ranging from 352 to 441 amino acids in length, there are three, which contain three repeats (3R-tau) and another three which has four repeats (4R-tau) **(Figure 7)**. 3R-tau to 4R-tau isoform ratio is 1:1 (for further reading see reviews 93-96).

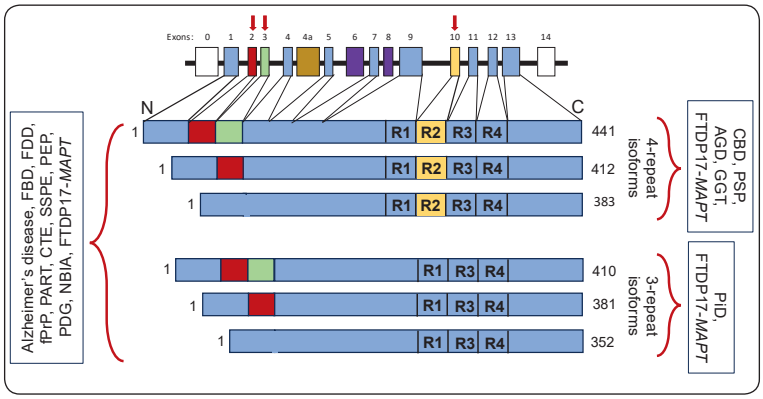

Figure 7. *The MAPT (tau gene), the six tau isoforms and their contributions to the different tauopathies. The MAPT gene (top row) consists of 14 exons and alternative mRNA splicing of exon 2 (highlighted in red), exon 3 (highlighted in green) and exon 10 (highlighted in yellow) results in the expression of six tau isoforms. As a result, three of the tau isoforms have four repeats (4-repeat tau/4R-tau) and three isoforms have three repeats (3-repeat tau/3R-tau) in their microtubule binding domain. In the largest group of tauopathies, represented by Alzheimer's disease, FBD, FDD, PART, fPrP, CTE, SSPE, PEP, PDG, NBIA, certain forms of FTDP17 MAPT, the filamentous tau inclusions consist of both 3R-tau and 4R-tau isoforms, in CBD, PSP, GGT, AGD and certain forms of FTDP17MAPT, which are 4R-tauopathies, only 4R-tau isoforms form the inclusions while in a third group, represented by Pick's diseae and certain forms of FTDP17MAPT the inclusions consist 3R-tau isoforms, hence the commonly used term is 3R-tauopathies. (R1, R2, R3, R4 denote the repeats in the microtubule binding domain of tau. The red vertical arrows point to the alternatively spliced exons. AGD = argyrophilic grain disease; CBD = cortocibasal degeneration; CTE = chronic traumatic encephalopathy; FBD = familial British dementia; FDD = familial Danish dementia; FTDP17 MAPT = frontotemporal dementia with parkinsonism linked to chromosome 17 MAPT; fPrP = familial prion diseases (certain forms); GGT = globular glial tauopathy; NBIA = neurodegeneration with brain iron accumulation (certain forms) PART = primary age-related tauopathy; PDG = parkinsonism dementia complex of Guam and the Kii paninsula; PEP = postencephalitic parkinsonism; PiD = Pick's disease; PSP = progressive supranuclear palsy; SSPE= subacute sclerosing panencephalitis)*

A fundamental feature of all tauopathies is an ordered assembly of post-translationally modified tau into insoluble filamentous inclusions of amyloid nature, which are further defined by their tau isoform composition and also by the molecular structure of the tau filaments[97, 98]. In a large group of diseases, the inclusions are exclusively formed by 4R-tau isoforms, and, in addition to CBD and PSP, this group also includes AGD, the globular glial tauopathies (GGTs) while 3R-tau isoforms form the characteristic inclusions (Pick bodies) in Pick's disease. Both 3R-tau and 4R-tau contributes to the inclusions in a third large group of neurodegenerative diseases, which importantly includes AD and also familial British dementia (FBD), familial Danish dementia (FDD), primary age-related tauopathy (PART), chronic traumatic encephalopathy (CTE), subtypes of familial prion diseases, the tauopathy associated with subacute sclerosing panencephalitis, postencephalitic parkinsonism and the Parkinsonism-Dementia Complex of Guam and the Kii Peninsula (PDG)[97]. In FTDP17 *MAPT*, the inclusions may be composed exclusively of 4R-tau, 3R-tau or both 4R-tau and 3R-tau, depending on the position of the mutation, which may result in amino acid substitutions or a change in the alternative splicing mechanism **(Figure 7)**[93, 97, 99–101].

Using Western blotting, the unique electrophoretic migration patterns of the insoluble tau in the different groups of tauopathies are defined by the isoform composition of the inclusions. In 4R-tauopathies, including CBD, PSP, AGD, GGT and certain forms of FTDP17 *MAPT*, the sarcosyl-insoluble tau forms two strong bands at 69kDa and 64kDa[102]. However, there are subtle differences in N-terminally cleaved tau fragments between CBD and PSP in that they form two closely related bands at ~37kDa in CBD and a single 33kDa band in PSP **(Figure 8)**[103, 104]. The doublet electrophoretic migration pattern found in 4R-tauopathies is different from the doublet pattern with two strong bands at 64kDa and 60kDa in 3R-tauopathies and also the characteristic triplet pattern with strong bands at 69kDa, 64kDa and 60kDa in tauopathies with 3R and 4R-tau[105].

The implementation of the cryo-electron microscope (cryo-EM) technique to the study of cerebral amyloid diseases, including the different tauopathies has transformed our knowledge about neurodegenerative diseases and also resulted in a new hierarchical, molecular classification of the tauopathies[93, 97–101, 106]. With this technique macromolecular structures such as amyloids are imaged

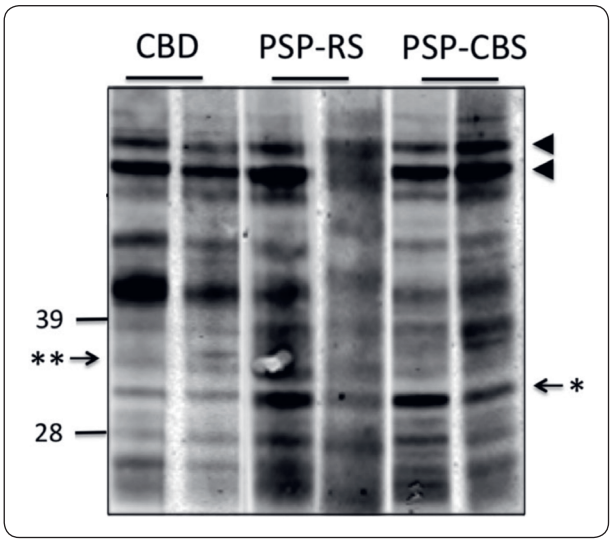

Figure 8. *Western blot analysis of disease-associated tau from frontal cortex homogenates of CBD and PSP cases. Sarcosyl-insoluble 4R-tau forms two strong bands at ~69kDa and ~64kDa (doublet pattern) in both CBD and PSP cases (arrowheads). However, the proteolytic fragments form a doublet at approximately 37 kDa (**) in CBD while there is a single band at approximately 33 kDa (*) in PSP. Numbers on the left indicate positions of molecular weight markers (kDa). (CBD-CBS: corticobasal degeneration with corticobasal syndrome; PSP-RS: progressive supranuclear palsy with Richardson's syndrome; PSP-CBS: progressive supranuclear palsy with corticobasal syndrome. Figure reproduced from Ling et al. Neuropathology and Applied Neurobiology 2014; 40: 149-163)*

in a frozen hydrated state with a transmission electron microscope using a highly sensitive 'direct electron detector'[107]. By combining information from numerous identical filaments, the overall filament structure with structural details at near-atomic resolution can be computed[108]. The cryo-EM studies of the different tauopathies resulted in several fundamentally important discoveries about the structure of the filament cores in the different tauopathies. As a consequence of this technique it has been recognised that the atomic structure of the protofilaments forming the filament cores in the 4R-tauopathies is such that incorporation of 3R-tau isoforms is incompatible into such assembles, which explains why 4R-tauopathies are exclusively composed of 4R-tau isoforms[97]. Importantly, it also has become clear that the cores of the tau filaments in each of the major 4R-tauopathies (CBD, PSP, AGD and GGT) have distinct structures[97]. For example, although essentially the same amino acid sequences make up the protofilaments in CBD and PSP, they adopt a four-layered fold in CBD (CBD fold) and a three-layered fold structure in PSP (PSP fold) **(Figure 9)**. These findings unequivocally confirm that, despite the clinical overlap between these two tauopathies, CBD and PSP are distinct, separate disease entities[97]. The novel findings about the filament structures in the different tauopathies are also consistent with the concept that unique disease-specific tau conformers or 'tau strains' define the different entities, including the 4R-tauopathies. This latter information, together with data provided by previous human and experimental transgenic animal studies, also underpin the hypothesis that a prion-like, neuron-to-neuron and region-to-region, stereotypic and anatomically determined propagation of the distinct 'tau strains' is a fundamental feature of the tauopathies, which also underlies clinical and pathological disease progression[52, 96, 109, 110].

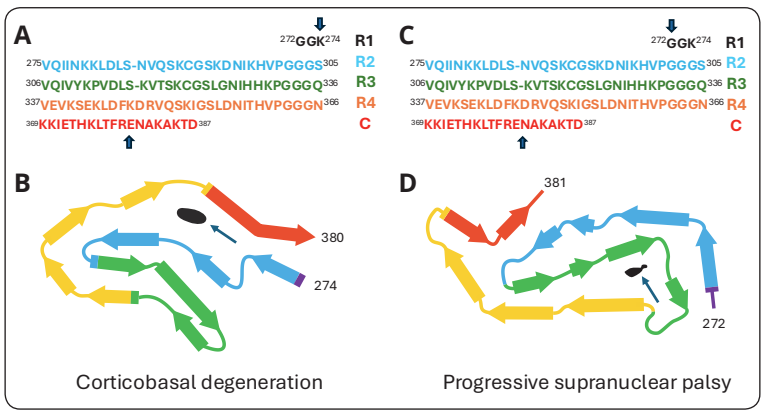

Figure 9. *Structures of tau filament cores in CBD and PSP.* **A** *and* **C:** *The protofilaments, determined by cryoelectron microscopy, comprise the last amino acid of the first repeat (lysine, residue 274) (R1: black) in CBD and three amino acids in PSP (starting with glycine, residue 272), the entire second repeat (R2: blue), third repeat (R3: green) and fourth repeat (R4: orange) in both diseases, and finally 12 amino acids C-terminal to R4 (C: red) in CBD, ending with glutamate at residue 380 and 13 amino acids ending with asparagine, at residue 381 in PSP.* **B** *and* **D:** *Despite near-identical amino acid sequences, the protofilaments adopt different conformations, a four-layered fold (CBD fold), which encloses a cavity with a large non-proteinaceous density (arrow) in CBD and a three-layered fold (PSP fold) with a smaller cavity and a non-proteinaceous density (arrow) in PSP. (The CBD and PSP protofilament images are the courtesy of Professor Michel Goedert, The Medical Research Council Laboratory of Molecular Biology, Cambridge, UK. CBD: corticobasal degeneration; PSP: progressive supranuclear palsy)*

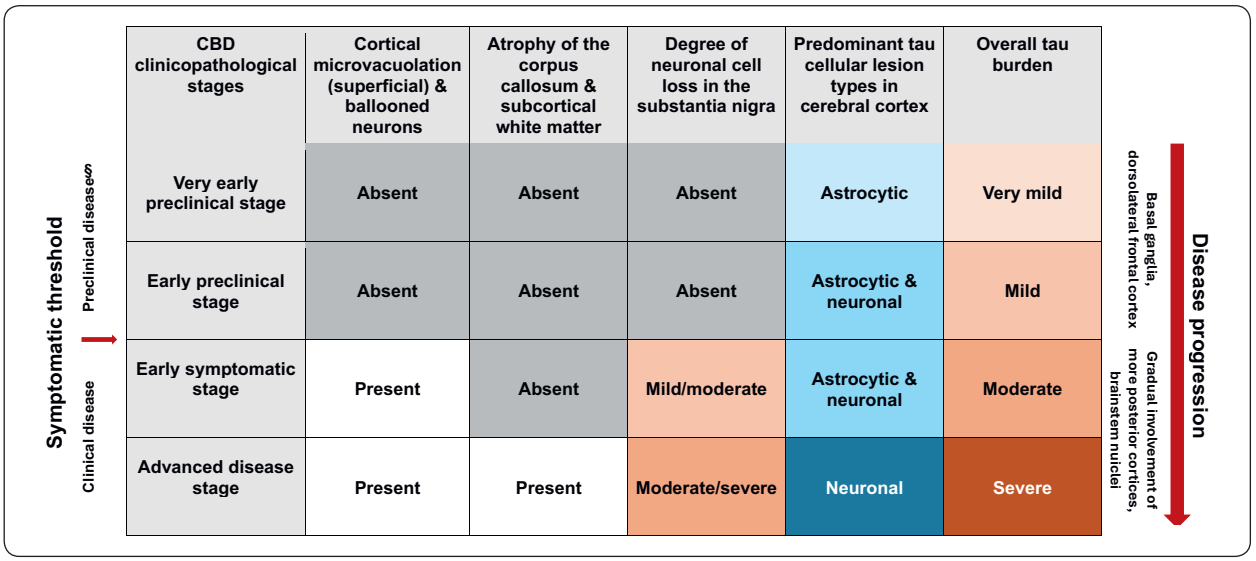

Figure 10. *Illustration of disease progression in CBD. A correlation is present between pathological changes, cortical microvacuolation, ballooned neurons (Pick cells), corpus callosum and subcortical white matter atrophy, severity of nigral cell loss, the predominance of tau cellular lesion types, the overall tau-burden and clinical disease stages, described as early preclinical, preclinical, early symptomatic and advanced disease. (Modified after Figure 7 in Ling et al. Brain 139:3237-52, 2016) (CBD: corticobasal degeneration)*

Pattern of progression of the tau pathology in CBD

Ample studies support the notion that the cerebral tau-burden is a reliable measure of the neurodegenerative process in AD and also in primary tauopathies, in which there is a dose-dependent clinicopathological correlation between neuronal tau deposition and clinical dysfunction[8, 52, 104, 111–113]. Furthermore, in several tauopathies, such as in AD[111], argyrophilic grain disease[114], Pick's disease[115] and PSP[116, 117] data also became available about the topographical pattern of progression of the tau pathology, which takes place via interconnected cerebral networks. However, until recently such information had remained unknown in CBD, which prompted our research group to address this issue. For this we used the large cohort of cases (N = 124) assembled from our own brain bank at the Institute of Neurology, Queen Square London and also from 13 other UK, European and US centres. Our CBD cohort included preclinical cases (preclinical CBD), cases with fully developed disease (end-stage CBD), a group of cases, in which death occurred due to an unrelated illness within 3 years or less of disease onset (intermediate CBD) and, finally cases with a rapidly progressive disease course (rapidly progressive CBD), who died of advanced disease within 3 years of disease onset (see also above)[8, 52].

By investigating a cohort of preclinical cases we could establish that striatal afferent connections to the dorsolateral prefrontal cortex and basal ganglia circuitry are likely to be the earliest neural network connections that are affected by tau deposition in CBD[52]. Our data, together with a few cases available in the liturature, support the notion that the earliest phase of the disease is followed by involvement of more posterior frontal areas while the substantia nigra is involved in the intermediate stage of the disease process. In advanced disease more posterior cortical involvement and neuronal loss become widespread[52]. The potential significance of the findings of our study for future *in vivo* imaging was emphasised by the scientific commentary that accompanied our publication[118].

Our studies also indicated that tau deposition, neuronal cell loss, neuropil microvacuolation and gliosis are time dependent pathological changes. For the assessment of whether neuronal or astrocytic tau deposition was specifically associated with different stages of disease progression, we determined a neuronal-to-astrocytic ratio as a measure of the relative severity of neuronal and astrocytic tau pathology. Using this ratio, we were able to show that astrocytic plaques are the predominant lesion type in the striatum and prefrontal cortex in the preclinical phase of the disease **(Figure 10)**. This could be of significance for the pathogenesis of CBD as the tau-positive astrocytic plaques have been shown to have a close spatial association with blood vessels[66]. Under normal circumstances astrocytes play a pivotal role in maintaining the barrier function of cerebral endothelial cells and malfuncion of the altered, tau-positive astrocytes may result in cofactors entering into the brain from the periphery, which could

trigger further tau assembly[119]. Our studies also showed that in the symptomatic disease phase there is a shift in cellular vulnerability from that seen in the preclinical cases, with neuronal tau deposition over astrocytic pathology becoming predominant, which underlies cerebral dysfunction manifesting in clinical symptoms and signs[8, 52].

Conclusions and future directions

The past 30 years have witnessed several major developments in the field of tauopathies, including CBD. Clinical diagnostic criteria and imaging characteristics of CBS have been established and many clinical variants with CBD underlying neuropathology have been identified. Understanding the underlying mechanisms of tauopathies was also facilitated by several important discoveries. These included that mutations of the *MAPT* gene result in familial tauopathies, which can closely mimick both clinical and neuropathological aspects of sporadic tauopathies, including CBD[44]. Furthermore genetic risk factors were identitifed in sporadic tauopathies, including CBD and PSP[41, 120–123]. A clear correlation has also emerged between the tau isoform composition of insoluble tau forming intracellular filamentous inclusions and the morphological phenotypic presentation in the different tauopathies[95]. Both animal and human studies have provided ample data supporting the notion that progression of the tau pathology is tau-strain and neural network-specific and that a prion-like mechanism may be responsible for the cell-to-cell and region-to-region spread of the tau pathology in the tauopathies[109]. To date, these scientific advances have not led to a successful disease modifying treatment trial for CBD, however our increasing knowledge and understanding of CBD provides a sound basis for the development of new therapeutic approahces.

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