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Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration

Abstract Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are usually sporadic multi-system degenerations associated with filamentous tau inclusions in neurons and glia. As such they can be considered sporadic tauopathies in contrast to familial tauopathies linked to mutations in the tau gene. Mutations have not been found in the tau gene in either PSP or CBD. The clinical syndromes and neuroimaging of typical cases of PSP and CBD are distinct; however,

atypical cases are described that have overlapping clinical and pathologic features. Both PSP and CBD have similar biochemical alterations in the tau protein, with the abnormal tau protein containing predominantly four-repeat tau. While there is overlap in the pathology in PSP and CBD, there are sufficient differences to continue the present day trend to consider these separate disorders. Several important pathologic features differentiate PSP from CBD. Ballooned neurons are frequent and nearly a sine qua non for CBD, but they are found in PSP at a frequency similar to that of other neurodegenerative diseases, such as Alzheimer's disease. Astrocytic lesions are different, with tufted astrocytes found in motor cortex and striatum in PSP and astrocytic plaques in focal atrophic cortices in CBD. The most

characteristic neuronal tau pathology in CBD is wispy, fine filamentous inclusions within neuronal cell bodies, while affected neurons in PSP have compact, dense filamentous aggregates characteristic of globose neurofibrillary tangles. Thread-like processes in gray and white matter are much more numerous and widespread in CBD than in PSP. The brunt of the pathology in CBD is in the cerebrum, while the basal ganglia, diencephalon and brainstem are the targets of PSP. Further clinicopathologic studies will refine our understanding of these disorders and open the possibility that common etiologic factors may be identified for these unusual sporadic tauopathies.

Key words Corticobasal degeneration · Progressive supranuclear palsy · Tau · Neuropathology

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Introduction

Progressive supranuclear palsy (PSP) is a multisystem degeneration characterized by neurofibrillary tangles (NFT) in the affected cell populations. It is one of the major causes of levodopa-nonresponsive Parkinsonism [67]. Many early cases of PSP present with unexplained falls and only later in the course does the characteristic clinical picture emerge, which features postural instability, vertical gaze palsy, axial rigidity, dysarthria and dementia [37]. PSP is an uncommon disorder, with prevalence rate estimates of about 1.5 per 100,000 [36], compared to 100 to 150 per 100,000 for Parkinson's disease

(PD). New cases occur at a rate of about 3 to 4 per million population per year [67].

Corticobasal degeneration (CBD) was first described in 1967 by Rebeiz as "corticodentatonigral degeneration with neuronal achromasia" [68]. While prevalence rates have not been estimated for CBD, it is less common than PSP. True prevalence rates would be difficult to estimate since the clinical and pathological spectrum of CBD is currently being refined, as evident in a number of recent clinicopathologic reports [54]. Original descriptions emphasized early and prominent asymmetrical movement disorder, but more recent reports have indicated that individuals with postmortem

findings of CBD may also have focal cortical syndromes, such as frontal lobe dementia or progressive aphasia [35, 54, 64]. This would suggest that the clinical phenotype of CBD is a reflection of the location of the dominant cortical pathology – with the classical phenotype corresponding to damage to the paracentral and superior frontal and parietal cortex. In cases with language abnormalities the brunt of the pathology is in the peri-Sylvian region.

Clinical differentiation of PSP and CBD

While not the primary focus of this presentation, a few words on the clinical features of PSP and CBD are warranted as a prelude to discussion of the differentiation of the two disorders pathologically. The most common initial sign of PSP is postural instability leading to falls and gait disturbance. [37]. Gait problems are progressive and disabling, leading eventually to confinement to chair or bed. CBD has a distinctly different presentation in typical cases. The initial signs are unilateral or asymmetrical apraxia, rigidity and dystonia. This may be associated with myoclonic jerks, grasp reflex, cortical sensory impairment and alien limb phenomenon. The affected hand may develop dystonic flexion contractures. Bradykinesia, rigidity, loss of facial expression, difficulty turning in bed or rising from a chair, loss of arm swing and reduced stride length that bring to consideration PD may be seen in both CBD and PSP; however, neither PSP nor CBD typically have a sustained clinical response to levodopa treatment.

Eye movement abnormalities are the hallmark of PSP and are characterized initially by impairment of downgaze, which is eventually followed by difficulties with upgaze and even horizontal gaze. There is usually striking preservation of the oculocephalic reflexes [37]. A supranuclear down-gaze palsy may develop in the course of CBD, but it is not usually as prominent as in PSP. These atypical cases warrant further clinicopathologic studies.

Other clinical features seen to varying degrees in PSP include dysarthria and dysphagia. Aphasia is rare or absent in PSP, but much more common in CBD. Some degree of mental dysfunction is the rule in PSP, although severe dementia is not usual. Attention is impaired and cognitive processing is slowed [25]. Frontal lobe dysfunction may be prominent [1,38, 57, 59]. Cognitive impairment is not universal in CBD, but more frequent than in PSP. It also has features of a frontal lobe dementia marked by personality change, disorder of conduct, impaired attention and distractibility. Frontal lobe signs, including grasp reflex, forced groping, utilization behavior and intermanual conflict, characteristically are unilateral at onset and markedly asymmetric in CBD. In contrast, asymmetry is unusual in PSP.

The alien limb phenomenon, which describes involuntary movement, such as elevation of the arm or leg into the air, is often emphasized in CBD, but it is neither specific to CBD nor found in many cases. Cortical sensory deficits due to parietal lobe involvement and characterized by graphesthesia and astereognosis are frequent in CBD, but decidedly uncommon in PSP, which largely spares posterior cortical regions.

Imaging studies in differentiation of PSP and CBD

Imaging studies are of limited use in the diagnosis of PSP. Narrowing of the anteroposterior midbrain diameter and dilation of the third ventricle are characteristic [37]. Structural imaging is more informative in CBD, where magnetic resonance imaging often shows asymmetrical atrophy of the superior parietal lobule variably extending into frontal regions, especially the superior frontal cortex.

SPECT and PET scanning show bilateral frontal hypoactivity in PSP [17, 30, 55]. The hallmark finding of such studies in CBD is asymmetry of hypometabolism in superior frontal and parietal lobes [6, 70]. Hypometabolism is sometimes also detected in caudate, putamen or thalamus in CBD. PET scans assessing dopamine metabolism [¹⁸F]-DOPA may show reduction of striatal and medial frontal uptake [70]. Striatal uptake is usually most severely impaired contralateral to the clinically most affected limbs. Symmetrical striatal dopaminergic deficits are found in PSP [5, 9].

Neuropathology of PSP

While the majority of clinically well-characterized patients with PSP have distinctive postmortem findings, there have been several reports suggesting that the match is not always perfect [13, 19, 33]. Gross examination of the brain may be unrevealing in PSP, but the most common pathological findings are midbrain atrophy, with dilation of the aqueduct of Sylvius and depigmentation of the substantia nigra. The locus ceruleus less often shows decreased pigment. The subthalamic nucleus may be noticeably smaller than expected and the superior cerebellar peduncle may be small. The external examination of the cerebral cortex may be normal, but mild atrophy in the frontal lobes, extending to the pre-central gyrus is not uncommon.

Microscopic findings include neuronal loss, fibrillary gliosis and NFT in basal ganglia, diencephalon and brainstem. A characteristic distribution is generally observed (Table 1) [28, 34, 40, 51]. The substantia nigra, globus pallidus and subthalamic nucleus are involved and demonstrate marked neuronal loss and reactive gliosis. The globus pallidus shows neuronal loss, gliosis, and NFT as well as iron pigment deposits and

Table 1 Neuropathologic differentiation of PSP and CBD

	PSP	CBD
Gross atrophy	Frontal, parasagittal or paracentral	Lobar (asymmetric, frontoparietal or paracentral)
Ballooned neurons	Rare (limited to limbic lobe)	Numerous in affected neocortical areas & limbic lobe
NFT	Globose & flame shaped Striatum Globus pallidus Basal nucleus Subthalamic nucleus Substantia nigra Oculomotor nuclei Raphe nuclei Locus ceruleus Pontine nucleus Tegmental gray Inferior olive	Mostly globose (so-called corticobasal bodies) Substantia nigra Locus ceruleus Raphe nuclei
Pick body-like tau inclusions	Dentate fascia	Cortex (layers II and III)
Neuropil threads	Present (sparse to many) Basal ganglia Internal capsule Thalamic fasciculus	Present (usually numerous) Cortex Cerebral white matter Internal capsule Pencil fibers in striatum Thalamic fasciculus Cerebral peduncle Tegmental fibers Pontine fibers
Glial lesions	Tufted astrocytes Coiled bodies (oligodendroglial)	Astrocytic plaques Coiled bodies (oligodendroglial)
Other pathology	Grumose degeneration of cerebellar dentate nucleus	Corticospinal tract degeneration

granular neuroaxonal spheroids. The striatum and thalamus, especially ventral anterior and ventrolateral nuclei, are also affected. The nucleus basalis of Meynert usually has mild cell loss, but more noticeable neurofibrillary pathology. The brainstem regions that are usually affected include the superior colliculus, periaqueductal gray matter, oculomotor nuclei, locus ceruleus, pontine nuclei, pontine tegmentum, vestibular nuclei and inferior olives. The cerebellar dentate nucleus is also frequently affected and may show grumose degeneration [2, 16, 60]. Spinal cord involvement is common although it is often not routinely studied [57].

Neuronal loss is usually greatest in the ventrolateral tier of the substantia nigra, as in PD [44], but there is often more extensive neuronal loss throughout all regions of the substantia nigra [50]. Neuronal cell loss is accompanied by fibrillary gliosis and globose-shaped NFT. Neuronal loss and NFT may be prominent in the globus pallidus. Large striatal neurons appear especially vulnerable, and loss of up to 30 to 40 % of these cells has been reported [63]. Neuronal loss in the basal nucleus of Meynert ranges from 13 to 54 % [77].

Cortical pathology is less pronounced, but frequent in the motor and pre-motor cortices [41, 42, 48, 81]. Early studies emphasized the lack of neocortical pathology in PSP [76], but more recent studies indicate consistent involvement of the frontal cortex in PSP [8, 41, 42, 81]. Neocortical NFT and glial tangles are concentrated in the precentral gyrus [41, 42].

Neurofibrillary pathology in the hippocampus is variable in PSP and not apparently intrinsic to the disorder, but rather more consistent with concurrent age-related pathology [8]. When present, the distribution of NFT in the hippocampal formation is qualitatively similar to that of AD. The exception to this rule is the frequent involvement of the dentate granule cells in PSP [42]. The degree of neurofibrillary degeneration may correlate with degree of cognitive impairment in PSP as in aging and AD [7].

While NFT in PSP often have a rounded or globose appearance, flame-shaped NFT are also detected. The Gallyas silver iodine method is sensitive to pathological structures in PSP and it demonstrates, in addition to NFTs, fibrillary inclusions in glial cells and cell processes. As in AD, NFT in PSP contain abnormally phosphorylated tau protein [27, 39, 47]. Immunocytochemistry for tau protein specifically demonstrates NFT in PSP, but also a wide variety of inclusions in both neurons and glia, including neuropil threads and tufts of abnormal fibers. The latter structures have been shown to be tau inclusions in astrocytes [49, 62, 84, 85]. Tufted astrocytes have a predilection for the frontal cortex areas and striatum and are often abundant in the precentral gyrus. Glial pathology accounts for much of the cortical pathology observed in PSP.

Tau immunohistochemistry also reveals tau-positive fibers [46, 66] and small round cells in the white matter of areas affected by PSP. The tau-positive cells in white matter, also referred to as “coiled bodies”, have been shown to be oligodendroglial inclusions [26, 49]. Some of the thread-like processes in white matter have been shown to be within both axons and the outer mesaxon of myelinated fibers. In gray matter tau-positive processes are much less common in PSP than in AD [18].

The NFT in PSP may be distinguished from NFT in AD by the paucity of ubiquitin immunoreactivity [4, 15]. Certain neurofilament epitopes may also distinguish NFT in PSP from those in AD [72]. A recent study with a panel of anti-tau antibodies recognizing epitopes along the length of the tau mole-

cule suggested that full length tau proteins are incorporated into the lesions in both AD and PSP [71].

Neuropathology of CBD

The gross examination of the brain usually shows narrowing of cortical gyri, most marked in pre- and post-central regions associated with widening of sulci, of greatest severity contralateral to the side of motor onset. This superior frontoparietal atrophy merges with less severe atrophy in anterior frontal and posterior parietal regions, while the temporal and occipital cortical regions are relatively preserved. The brainstem and cerebellum are not consistently reduced in size, but horizontal sectioning of the brainstem shows loss of pigment in the substantia nigra and mild atrophy of the midbrain tegmentum with enlargement of the aqueduct.

In affected areas, especially the superior frontal gyrus, swollen and vacuolated cortical neurons, referred to as ballooned neurons (BN), are scattered in the third, fifth and sixth cortical layers. BN may be found in large numbers in anterior cingulate, amygdala and claustrum; and in smaller numbers in posterior cingulate, temporal, insular, parietal and frontal cortex. They are much less frequently found in striatum, thalamus and hippocampus and have not been reported in calcarine cortex or cerebellum. BN are eosinophilic and weakly argyrophilic, and they lack apparent Nissl substance. They often have swollen proximal dendrites. Some are vacuolated, and granulovacuolar bodies may be found in BN. Rebeiz and colleagues called this appearance neuronal achromasia, a term which they extended to cover subcortical swollen cells, and to nigral and brainstem neurons with ill-defined inclusions. The BN are analogous to "Pick cells" in Pick's disease [23]. BN are strongly immunoreactive for phosphorylated neurofilaments [24, 73] and variably reactive for tau protein. BN also show reactivity for α B-crystallin [58], and sometimes for ubiquitin and tau [26, 73], but not for epitopes specific to neurofibrillary tangles [24]. Ultrastructurally, the cytoplasm of the ballooned neurons contains rather disorderly accumulations of filaments 9–16 nm in diameter, interspersed with other cytoplasmic elements [12].

On microscopic examination, sections of atrophic frontoparietal cortex show moderately severe nerve cell loss and subcortical myelin pallor with gliosis. There is disruption of the normal pattern of cortical lamination, superficial spongiosis and diffuse astrocytic and microglial proliferation. Atrophic cortical areas consistently contain scattered argyrophilic neuronal inclusions in the second and third layers, which are similar to pleomorphic Pick bodies or small NFT [26, 52]. The neuronal inclusions in CBD differ from Pick bodies in that they are more fibrillar, not always round and less well circumscribed. Pick bodies are abundant in the granule cell layer of the dentate gyrus of the hippocampus, an area relatively

unaffected in CBD. As in PSP, affected white matter has tau-positive cell processes and oligodendroglial inclusions, but they are more numerous and widespread in CBD than in PSP. In contrast to AD, where tau positive processes are limited to gray matter, in CBD the white matter also is severely affected.

The substantia nigra usually shows moderate to severe nerve cell loss with extraneuronal neuromelanin and gliosis. Many of the remaining neurons contain ill-defined neurofibrillary inclusions, so-called "corticobasal bodies" [35]. These inclusions have a homogeneous or whorled appearance and granules of melanin tend to become enmeshed in some of them. They are essentially indistinguishable from globose tangles of PSP. The locus ceruleus and raphe nuclei have similar inclusions. In contrast to PSP where neurons in the pontine base almost always have at least a few NFT, the pontine base is largely free of NFT in CBD. On the other hand, tau inclusions in glia and in cell processes are frequent in the pontine base in CBD. NFT are also detected in the tegmental gray matter.

In other subcortical regions the globus pallidus and putamen show nerve cell depletion with gliosis and occasional NFT. The nucleus basalis of Meynert has a few NFT. The red nucleus and subthalamic nucleus also show mild neuronal depletion and astrocytic gliosis and may have NFT. Thalamic nuclei may also be affected, particularly the ventrolateral nucleus. Mild neuronal depletion of the dentate nucleus occurs, but grumose degeneration is much less common than in PSP.

The Gallyas silver stain is a sensitive way of demonstrating pathology in neurons and glia in CBD [43]. With this technique the tangles vary from wispy fragments to densely silver impregnated inclusions. Immunocytochemistry with monoclonal antibodies shows that many inclusions have positive reactions to epitopes in phosphorylated neurofilaments and tau [61, 64, 82]. The glial lesions in PSP and CBD are distinctive as seen in these sections stained with the Gallyas method. Glial inclusions in neurodegenerative disorders have been the subject of a recent review [11]. The characteristic pathology in CBD is in cell processes – distal cellular domains – while in PSP it is in cell bodies – proximal cellular domains [26]. The abnormal astrocytic lesions in CBD are characterized by stubby tau-positive processes radially arranged around a central astrocyte. Because the lesions are reminiscent of neuritic plaques in AD, but they lack amyloid, they are referred to as astrocytic plaques [26]. The abnormal astrocytes in PSP appear as irregular fibrous tufts and have been referred to as tufted astrocytes [22].

Ultrastructural differences between PSP and CBD

While NFT in AD are composed mostly of 22-nm diameter paired helical filaments (PHF) and a minor component of 15-

to 18-nm diameter straight filaments [79], similar studies of NFT in PSP show mostly straight filaments [10, 65, 69, 78, 83]. In addition astrocytes in PSP contain straight filaments [62]. In CBD the filaments, like those in AD, have a paired helical appearance, but the diameter is wider and the periodicity is longer. These structures have been referred to as twisted ribbons. Studies of their mass per unit length also show differences in the filaments in CBD compared to AD [53].

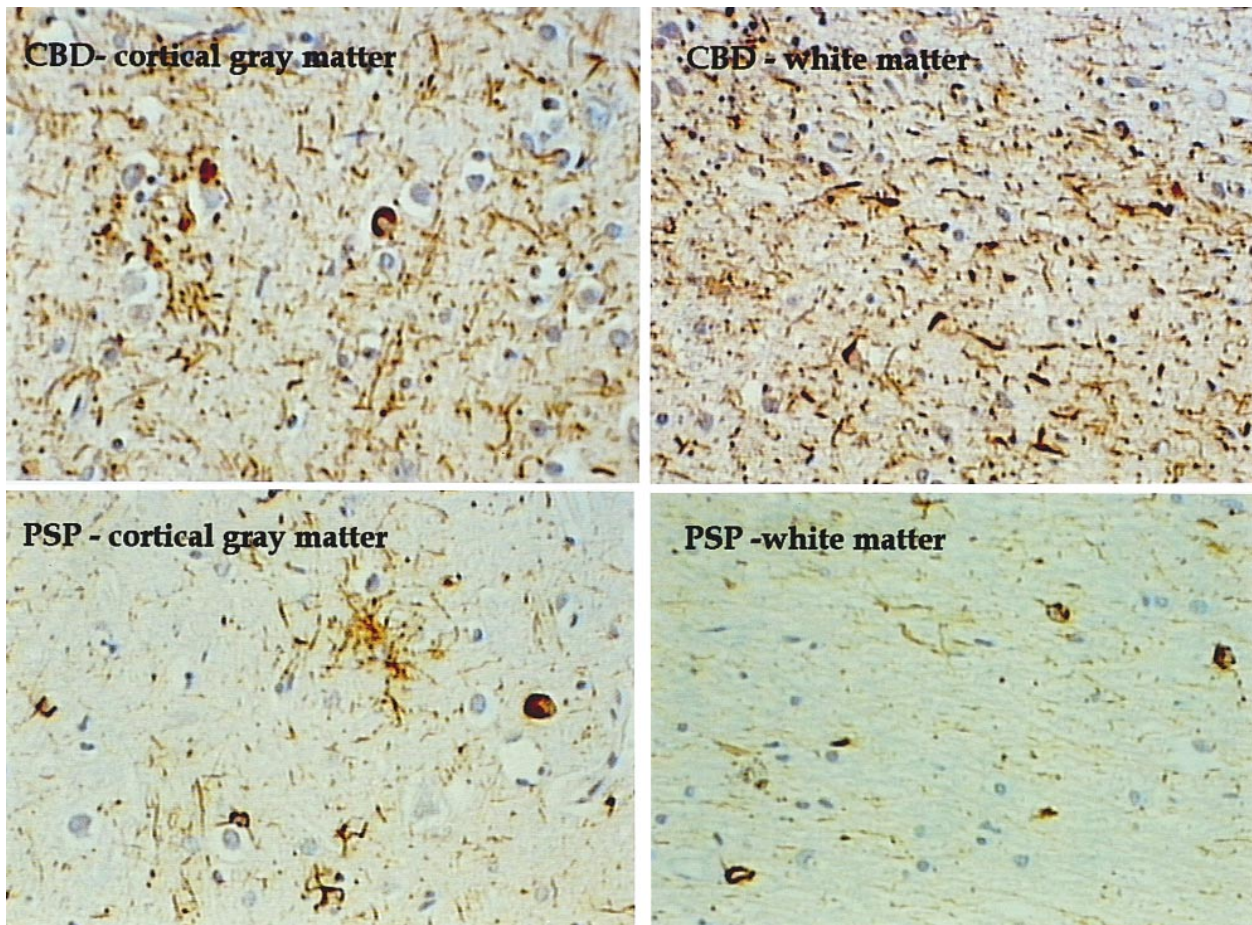
Molecular biology of tau protein in CBD and PSP

Biochemical methods distinguish the tau protein abnormalities in AD from PSP. Western blots of detergent-insoluble tau, which is a pathologic form of tau not detected in normal brains, from AD brain reveal three tau-immunoreactive bands of 60, 64, and 68kD. In contrast, similar detergent insoluble proteins from PSP shows a characteristic doublet of 64 and 68 kD [29, 81]. Interestingly, the entorhinal cortex of PSP brains contained not the doublet characteristic of PSP, but the triplet found in AD material. These results support the suggestion that

allocortical pathology in PSP is similar to that in AD. After dephosphorylation, the pathologic tau proteins in PSP are composed almost exclusively of tau with four repeats with respect to the conserved repeats in the carboxyl half of the molecular that form the microtubule-binding site. In contrast, the pathologic tau protein from AD has both three and four repeat isoforms.

Biochemical studies of tau protein in CBD are few, but it also is a disorder characterized by two major tau isoforms, as in PSP [53]. While initial studies suggested that the doublet in PSP was different from the doublet in CBD, more recent studies using dephosphorylation shows that pathologic tau protein in CBD, like PSP, is composed of four repeat tau [75]. Given the fact that the major difference between three and four

Fig. 1 Tau immunostaining of cerebral cortex and white matter in a case of CBD and another of PSP. Note the presence of numerous thread-like processes in both the gray and white matter in CBD. In contrast, PSP has fewer threads and more inclusions in cell bodies of neurons and glia. A prominent tufted astrocyte in the gray matter and several coiled bodies are readily apparent in PSP.



repeat tau is alternative splicing of exon 10, these observations are of interest. Several of the mutations in tau in FTDP-17 specifically affect alternative splicing of exon 10 [45]. Thus, PSP and CBD, which are mostly sporadic disorders, may share similar mechanisms of pathogenesis with respect to abnormal tau isoforms. Further studies of the pathogenesis of these well-defined genetic diseases may shed light on the more common sporadic diseases.

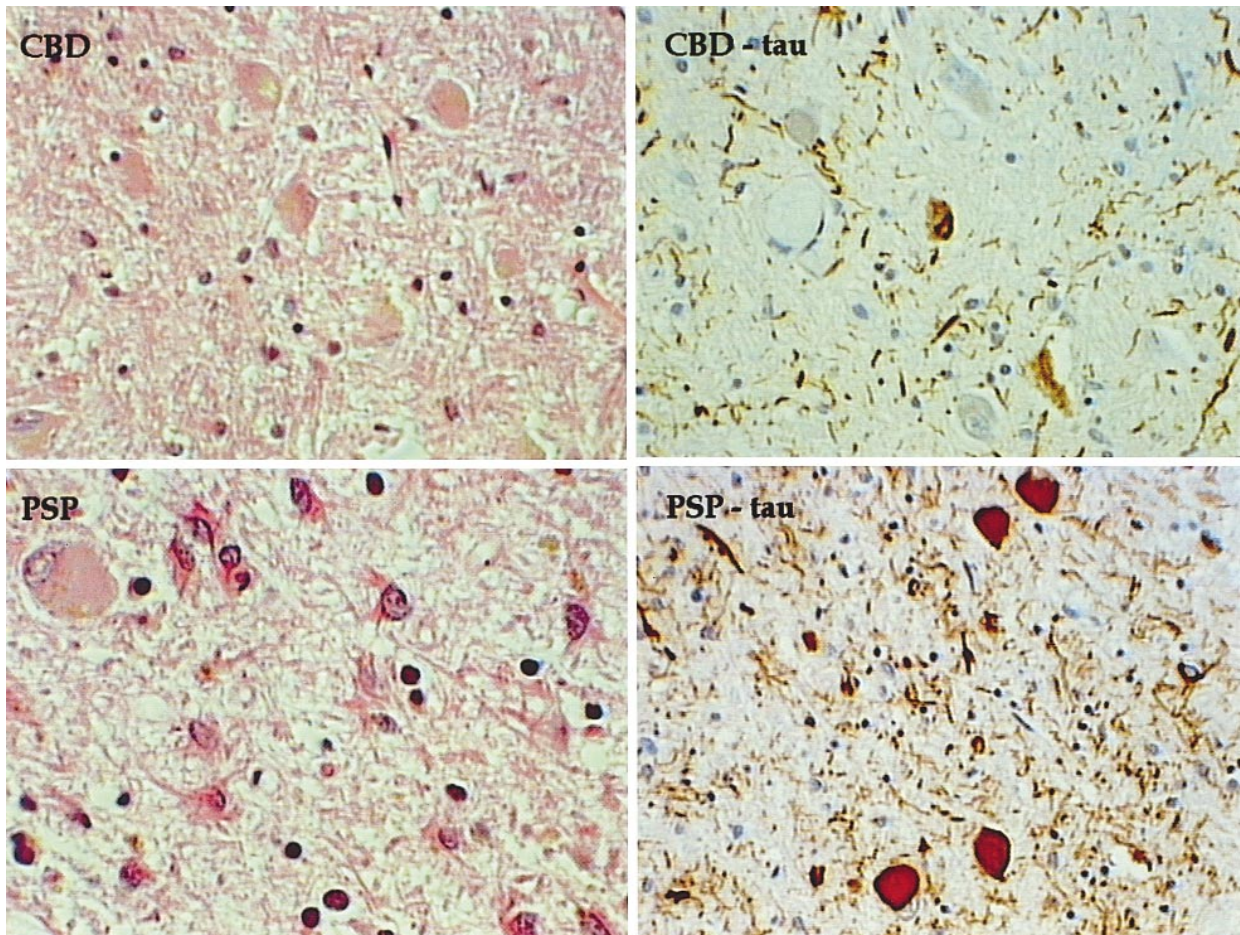
Etiology of PSP and CBD

The etiology of PSP is unknown, but as in many neurodegenerative diseases a multifactorial causation is implicated. Genetic influences are increasingly suggested. Although there are only a few reports of autopsy-proven familial PSP [21, 32, 80], recent studies have revealed a genetic polymorphism in the tau gene associated with greater than chance frequency with PSP [14]. The initial observation of a single polymorphism in tau in PSP has been confirmed in several studies and more recently the initial observations have been discovered to

reflect an extended haplotype of the tau gene [3]. Essentially two forms of the tau gene have been defined – H1 and H2. Most cases of typical PSP are H1 and a surprising large number of PSP patients are H1/H1 homozygous. There is some preliminary evidence to suggest greater variability in the disease phenotype in PSP cases that are heterozygous (H1/H2). CBD also appears to be associated with increased frequency of H1 haplotype, but this observation is based upon a much smaller sample size.

Almost all reported cases of CBD have been sporadic, but there are rare familial reports of CBD. In addition the fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) shares a number of pathologic features with

Fig. 2 Sections of the subthalamic nucleus of Luys in a case of CBD (top row) and PSP (bottom row) stained with H&E (left) and tau (right). The neurons are preserved in the subthalamic nucleus of CBD, but there is marked neuronal loss and dense fibrillary gliosis in PSP. A residual neurons in the PSP case have a globose NFT. More numerous NFT are visible with tau immunostaining. In CBD, tau immunostaining reveals thread-like processes and punctate to finely fibrillary inclusions in small neurons.



PSP and CBD. In particular, familial multi-system tauopathy reported by Ghetti and familial pedunculo-pontine degeneration have many histological, ultrastructural and biochemical similarities [74]. These disorders are clearly linked to a gene on chromosome 17 [31], and recent studies have implicated tau as the gene. In particular, mutations in the coding and non-coding regions of the tau gene have been identified in some families with FTDP-17 [45].

Environmental factors are suspected to play a role in the causation of PSP, but a case-control study has failed to identify a factor or factors that might be responsible. In particular, pesticide exposure, well-water use, nonsmoking and head trauma were not associated with increased risk of PSP [20, 37]. Comparable case-control studies of environmental factors have not been conducted for CBD.

Differential diagnosis

While there is considerable overlap in the pathology in PSP and CBD. The two disorders can usually be readily distinguished. In CBD the brunt of the defining pathology is in the cortex and cortical white matter (Fig. 1). BN are nearly a sine qua non for CBD, but are quite uncommon in PSP, except in the limbic gray matter, where BN can be found in a number of degenerative disorders, including AD. While there is no disputing the fact that cortical pathology is found in PSP, the brunt of the pathology of PSP is subcortical, with particularly severe disease in the pallido-Luysial-nigral axis (Fig. 2). In PSP, tau is prominent in cell bodies in neurons and oligodendroglia, and astrocytes in the cortex and striatum. In CBD, tau is most abundant in cell processes (Fig. 3). Table 1 summarizes the major differences.

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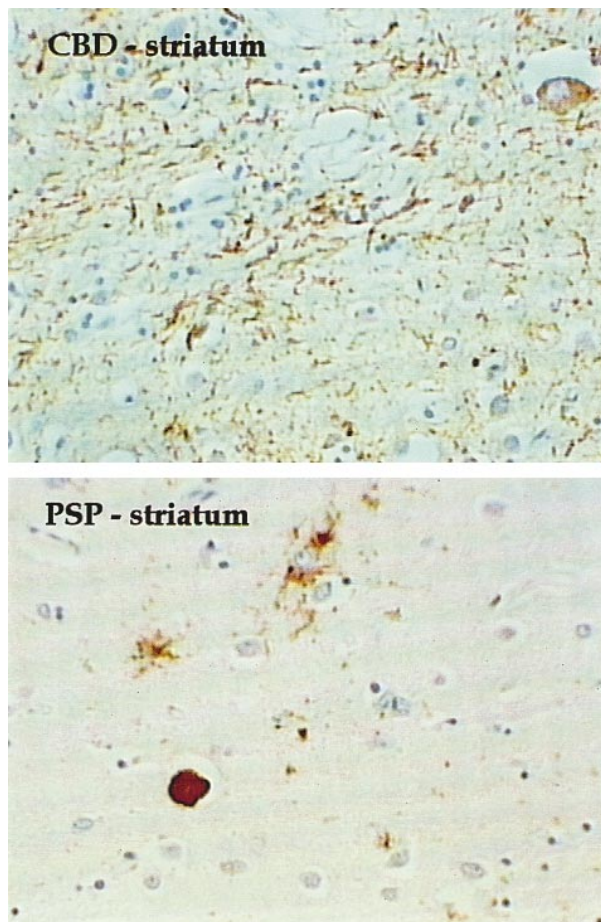


Fig. 3 The corpus striatum in CBD and PSP present different pathologies. In CBD the predominant finding on tau immunostained sections is numerous thread-like processes in gray and white matter, especially in the pencil fibers. In contrast globose NFT and tufted astrocytes are found in PSP with only sparse thread-like processes.

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