**ABSTRACT:** Tauopathies are a group of disorders that have in common abnormal accumulation of tau protein in the brain. Although the different tauopathies have long been considered to be separate diseases, it is now clear that progressive supranuclear palsy, corticobasal degeneration and some forms of frontotemporal lobar degeneration share clinical, pathological and genetic features. The important overlap between these disorders suggest they may represent different phenotypes of a single disease process, the clinical result depending on the topography of pathological lesions as well as other unknown factors.

**RÉSUMÉ:** Tauopathies : une ou plusieurs maladies? Les tauopathies sont un groupe de maladies qui ont en commun une accumulation anormale de protéine tau dans le cerveau. Bien que les différentes tauopathies ont longtemps été considérées comme des maladies distinctes, il est clair maintenant que la paralysie supranucléaire progressive, la dégénérescence corticobasale et certaines formes de dégénérescence loboïde frontotemporale ont des caractéristiques cliniques, pathologiques et génétiques communes. Le chevauchement important entre ces maladies suggère qu’elles pourraient être des phénotypes différents d’un processus pathologique unique dont le résultat clinique dépend de la topographie des lésions anatomopathologiques ainsi que de facteurs inconnus.


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**Tauopathies: One Disease or Many?**

Manon Bouchard, Oksana Suchowersky

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Tauopathies refer to a group of disorders that have in common the accumulation of insoluble hyperphosphorylated tau protein in the brain. More than 20 different degenerative disorders are characterized by some degree of neurofibrillary degeneration and can be classified as tauopathies. In prototypical tauopathies like progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease or frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), tau inclusions are the sole or predominant central nervous system lesions, whereas in other conditions like Alzheimer disease (AD), Down syndrome or myotonic dystrophy, tau aggregates are found in association with other major neuropathological abnormalities such as amyloid deposition. Most tauopathies cause dementia, often combined with some degree of extrapyramidal dysfunction.

Tau proteins belong to the family of microtubule-associated proteins and are found mostly in neurons and to a lesser extent in oligodendrocytes and other non-neural tissues. This protein is involved in stabilization and assembly of microtubules. In the adult human brain, six tau isoforms are produced by alternative messenger ribose nucleic acid (mRNA) splicing of a single gene located on chromosome 17q21. Alternative splicing of exons 2 and 3 results in tau isoforms that differ by the presence of one or two amino-terminal inserts, whereas alternative splicing of exon 10 affects the number of microtubule-binding repeats. Three isoforms with three microtubule-binding repeats (3R) excluding exon 10 and three isoforms with four microtubule-binding repeats (4R) including exon 10 are found in equal amounts in the normal brain. The relative amount of each isoform (3R or 4R) can vary with certain diseases. In AD, insoluble tau contains both 3R and 4R isoforms, whereas in Pick disease we find predominantly 3R-tau accumulation and in PSP or CBD, 4R-tau aggregates dominate.

The distinction between tauopathies that were once considered to be distinct diseases are beginning to blur. It is now recognized there is considerable overlap in the clinical and pathological features of PSP, CBD and some forms of frontotemporal lobar degeneration (FTLD). Recent genetic and pathological findings suggest common molecular mechanisms for CBD and PSP. Such considerations suggest these disorders should be viewed as part of the same disease spectrum.

This review will discuss the typical and atypical clinical and pathological presentations of PSP, CBD and some forms of FTLD, focusing on their overlapping features. Recent genetic and molecular findings supporting a common background for these disorders will also be reviewed.
**Table 1: Most prevalent tauopathies. (Modified from Williams, Intern Med J 2006)**

<table>
<thead>
<tr>
<th>Predominantly tau pathology</th>
<th>Pattern of dementia</th>
<th>Movement disorder</th>
<th>3R:4R</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSP</td>
<td>Frontal dysexecutive, PNFA</td>
<td>Axial disorder with postural instability and ophthalmoplegia or asymmetric parkinsonism</td>
<td>1:2-4</td>
</tr>
<tr>
<td>CBD</td>
<td>Parietal, frontal dysexecutive, PNFA</td>
<td>Asymmetric parkinsonism, dystonia, myoclonus or tremor, alien limb</td>
<td>1:2</td>
</tr>
<tr>
<td>Argyrophilic grain disease</td>
<td>Limbic dementia</td>
<td>No</td>
<td>1:2</td>
</tr>
<tr>
<td>Pick disease</td>
<td>Frontal dysexecutive, PNFA, SD</td>
<td>Rare</td>
<td>3:1</td>
</tr>
<tr>
<td>FTDP-17</td>
<td>Frontal behavioural or amnestic</td>
<td>Variable parkinsonism, can be PSP-like or CBD-like</td>
<td>1:2, 1:1 or 2:1</td>
</tr>
<tr>
<td>Post encephalitic parkinsonism</td>
<td>Rare</td>
<td>Symmetric rigidity with bradykinesia, ophthalmoplegia</td>
<td>1:1</td>
</tr>
<tr>
<td>Parkinsonism-dementia complex of Guam</td>
<td>Frontal dysexecutive, cortical</td>
<td>Symmetric rigidity with bradykinesia, ophthalmoplegia</td>
<td>1:1</td>
</tr>
<tr>
<td>Guadeloupean parkinsonism</td>
<td>Frontal dysexecutive</td>
<td>Symmetric rigidity with bradykinesia, ophthalmoplegia</td>
<td>1:2</td>
</tr>
</tbody>
</table>

**Associated with amyloid deposition**

| Alzheimer disease                            | Amnestic, cortical                      | Rare                                                                            | 1:1   |
| Down syndrome                                | Amnestic, cortical                      | No                                                                              | 1:1   |
| Dementia pugilistica                          | Amnestic, cortical                      | Parkinsonism                                                                    | 1:1   |
| Familial British dementia, familial Danish dementia | Amnestic, cortical                  | No                                                                               | -     |

**In association with other pathology**

| Myotonic dystrophy                           | Frontal behavioural                     | No                                                                               | 2:1   |
| Hallervorden-Spatz disease                    | Mental retardation                      | Gait disturbance, extrapyramidal syndrome                                        | -     |
| Niemann Pick type C                           | Mental retardation                      | Dystonia, ataxia, ophthalmoplegia                                               | -     |
| SSPE                                        | Mental regression                       | Myoclonus, ataxia, late rigidity                                                | -     |

PSP, progressive supranuclear palsy; PNFA, progressive non fluent aphasia; CBD, corticobasal degeneration; SD, semantic dementia; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; SSPE, subacute sclerosing panencephalitis

**Progressive Supranuclear Palsy**

**Typical clinical presentation - Richardson syndrome**

Progressive supranuclear palsy is the second most common form of parkinsonism after idiopathic Parkinson disease. This neurodegenerative condition was first described in 1964 by Steele, Richardson and Olszewski as an “unusual syndrome” characterized by a combination of progressive postural instability with axial rigidity, supranuclear gaze palsy, mild dementia and pseudobulbar palsy, without tremor or limb bradykinesia and rigidity. Since the first description almost 50 years ago, many more case reports lead to a better description of the clinical presentation. The most important clinical features for diagnosis of PSP, as stated in the NINDS-SPSP diagnostic criteria, are the presence of early and prominent postural instability leading to falls and supranuclear gaze palsy (SNGP), along with a progressive course. As SNGP with difficulty looking either up or down generally develops years after disease onset, this is not useful for early diagnosis, although impairment of vertical and horizontal saccades and presence of square wave jerks can be early diagnostic clues. Patients with PSP typically exhibit axial rigidity, slurred speech, swallowing difficulties, eyelid retraction with staring gaze, sometimes associated with dystonic retrocollis, blepharospasm or eyelid opening apraxia. Many recent reports have shown that not only dysarthria, but also non fluent aphasia and apraxia of speech were common in PSP. Neuropsychiatric symptoms develop in more than half the patients within two years of disease onset and include subcortical dementia with prominent cognitive slowing, poor recall, attention and frontal executive deficits, along with personality changes such as apathy, irritability and disinhibition, a profile mimicking bifrontal lobe disease. Following symptom onset, patients with PSP experience a relentless progression with death within five to eight years.

**Atypical clinical presentations**

Following the early descriptions of typical Richardson syndrome, there have been a number of cases reported with pathological findings of PSP but atypical clinical presentations, suggesting there is a great clinical variability among patients with PSP pathology. Although SNGP was considered in the NINDS-SPSP criteria to be a mandatory finding for a clinical diagnosis of PSP, we now know that many patients with this condition never develop eye movement abnormalities. Some individuals present with asymmetric rigidity, tremor and a moderate response to levodopa mimicking idiopathic Parkinson disease (PD), or with asymmetrical cortical symptoms mimicking CBD, such as apraxia, alien limb, arm levitation or hemidystonia. Cognitive decline and behavioural changes are the presenting complaint in 15% to 30% of cases and can remain the only clinical feature throughout the disease. Many case reports and series describe patients with an ultimate pathological diagnosis of PSP presenting with isolated apraxia of
speech or progressive non fluent aphasia\cite{16,34-40}. Some of these cases later developed mild parkinsonism, apraxia or eye movement abnormalities, but others had an isolated speech disturbance until death\cite{34-36}.

Williams et al\cite{10} have recently suggested a new classification to account for the different clinical presentations of pathologically proven PSP. They have described five distinct presentations of PSP: Richardson syndrome (the classic clinical picture of PSP), PSP-parkinsonism (asymmetrical onset of limb rigidity and bradykinesia with or without tremor and levedopa response), pure akinesia with freezing of gait, PSP presenting as a corticobasal syndrome and PSP presenting as apraxia of speech or progressive non fluent aphasia (Table 2).

The clinical heterogeneity of PSP leads to common diagnostic errors. Clinicopathologic studies have shown that only 35% to 64% of patients with PSP pathology at autopsy had an accurate clinical diagnosis during life\cite{21,24,34,35}. Alternate clinical diagnosis include CBD, PD, primary progressive aphasia, FTLD, AD and cerebrovascular disease\cite{21,24,34,35}.

### Other conditions mimicking the PSP syndrome

A number of neurodegenerative conditions can mimic the symptoms of PSP, leading to clinical misdiagnosis. Among patients with a PSP-like clinical picture, only 62% to 91% do have PSP pathology at autopsy\cite{35,41-43}. The disorders most commonly mistaken for PSP during life are CBD, PD with concomitant AD or lewy body pathology, multiple system atrophy, AD and FTLD\cite{20,35,41-44}.

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**Table 2: Clinical presentations of PSP. (Adapted from Williams, Lancet Neurol 2009)**

<table>
<thead>
<tr>
<th></th>
<th>Rigidity</th>
<th>Bradykinesia</th>
<th>Tremor</th>
<th>Postural instability</th>
<th>Early cognitive decline</th>
<th>Eye movement abnormalities</th>
<th>Levo-dopa response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Richardson syndrome</strong></td>
<td>Axial &gt; limbs</td>
<td>Mild</td>
<td>No</td>
<td>Yes, early falls</td>
<td>Frontal dysexecutive, behavioural, AOS, PNFA</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>PSP-parkinsonism</strong></td>
<td>Axial ≤ limbs</td>
<td>Moderate</td>
<td>Possible</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td><strong>Pure akinesia with gait freezing</strong></td>
<td>Axial</td>
<td>Moderate</td>
<td>No</td>
<td>Yes, with freezing of gait</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>PSP-CBS</strong></td>
<td>Asymmetrical</td>
<td>Asymmetrical</td>
<td>No</td>
<td>Possible</td>
<td>Unilateral parietal, frontal dysexecutive, PNFA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>PSP-PNFA</strong></td>
<td>Possible</td>
<td>Mild</td>
<td>No</td>
<td>Possible</td>
<td>PNFA, frontal dysexecutive</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

AOS, apraxia of speech; PNFA, progressive non fluent aphasia; CBS, corticobasal syndrome; PSP, progressive supranuclear palsy.
Typical pathology of PSP

Macroscopically, the pathological findings of PSP include predominant midbrain atrophy, some degree of atrophy of the pallidum, thalamus, and subthalamic nucleus and mild symmetric frontal atrophy.9,45. Histopathology is characterized by accumulation in the brain of abnormal 4R-tau protein within neurons (globose and flame-shaped neurofibrillary tangles and neuropil threads) and glial cells (tufted astrocytes, thorn-shaped astrocytes and coiled bodies).34,46,47. The distribution of tau inclusions is mainly subcortical in the globus pallidus, subthalamic nucleus, substantia nigra and brainstem, which are severely affected in most cases.34,46,48. Tau pathology also occurs in a lesser extent in the dentate nucleus of the cerebellum.46,48. Cortical involvement is a common finding in PSP although not considered so initially.46. Motor and premotor cortices typically show abundant tufted astrocytes whereas some neurofibrillary tangles or pre-tangles can be found in the hippocampus and frontal or insular cortices.15,24,46,47. The classic Richardson syndrome is the most commonly associated with such typical PSP pathology.10.

Atypical pathology of PSP

Atypical pathological cases of PSP are variants in which the severity or distribution of abnormalities deviate from the typical pattern.46. For example, some cases of PSP have been described with severe neocortical involvement in addition to typical or milder subcortical pathology; these patients tend to present with asymmetrical cortical symptoms such as apraxia, alien limb phenomenon or progressive aphasia, with or without the expected symptoms of PSP.34,36,49,53. Other patients tend to have a more restricted pattern of distribution of tau pathology with less involvement of the motor cortex, striatum, pontine nuclei and cerebellum; such individuals usually present with prominent gait instability without dementia or SNGP.40,54,55. Another variant has been described where tau burden is less severe although with a similar distribution as in Richardson syndrome, leading to a slower disease progression and a clinical picture resembling PD.10,54,56. Therefore, it appears that the severity and distribution of tau pathology in PSP are responsible for the variability in clinical presentation.

Corticobasal Degeneration

Typical clinical presentation - The corticobasal syndrome

The first report of three patients who developed a syndrome called “corticodentatonigral degeneration with neuronal achromasia” characterized by progressive asymmetric slowness and awkwardness of voluntary movements with superimposed involuntary movements and late cognitive dysfunction was published in 1967.57. Twenty years later, the name “corticobasal degeneration” was introduced by Gibb et al to describe the same disorder.58. The clinical hallmark of CBD is a combination of progressive cortical and extrapyramidal dysfunction, the latter being unilateral at onset and remaining very asymmetrical until death (also called “corticobasal syndrome” (CBS)). Basal ganglia involvement manifests as asymmetric akinesia, rigidity, dystonia, myoclonus, tremor or any combination of the above; cortical features include alien limb phenomenon, ideomotor apraxia, cortical sensory loss or aphasia.58-60. Patients with CBD do not have a dramatic response to levodopa therapy.

For many years, dementia was considered an atypical finding in patients with CBD,61 but more recent studies have shown that dementia is present in 35-70% of patients at onset and eventually develops in everyone.63. Cognitive dysfunction is of the “frontal” type with impairment in executive functions, set-shifting tasks, attention and visuospatial tasks.20,64,65. Depression, apathy, irritability, disinhibition and other personality changes similar to those found in the behavioral variant of frontotemporal dementia are also common.20,63,66. Speech and language complaints are frequently noted at onset and eventually develop in 90-94% of patients later in the disease.59,67,68. Speech disturbances manifest as progressive non fluent aphasia, apraxia of speech, dysarthria, dysphonia or sometimes mutism.16,20,59,67,68. Over time, most patients develop oculomotor apraxia and postural instability.59.

Atypical clinical presentations

Apart from the classical syndrome, patients with pathologically-proven CBD can present with a variety of different clinical pictures. Clinical misdiagnosis occurs in 47-69% of patients.35,59,69 and is associated with the lack of expected features (apraxia, alien limb, dystonia, parkinsonism) or the presence of unexpected findings (early prominent gait disorder or supranuclear gaze palsy). Common erroneous diagnosis include PSP, FTLD, AD, progressive non fluent aphasia, PD or Lewy body dementia (LBD).35,59,69,70. The early clinical presentation of CBD can be either motor or neuropsychiatric.63. Some patients present with prominent gait disorder, falls and eye movement abnormalities suggesting a diagnosis of PSP.29,35,44,58,60. However, the majority of patients with pathologically-proven CBD do not present with a movement disorder but rather with isolated cognitive, behavioral or language changes.20,60,69. Cognitive and personality changes typically suggest frontal dysfunction similar to that seen in FTLD, but some cases exhibit a posterior cortical atrophy syndrome (Balint or Gerstmann syndromes, visual agnosia, agraphia, alexia)\textsuperscript{71,72}. Progressive aphasia or apraxia of speech are particularly common presenting features.16,73,74 and were the presenting symptom in 25% of the cases reviewed by Wadia and Lang.60. Most patients who present initially without extrapyramidal features develop them over time, either early or late in the disease process. Some cases never exhibit clinically significant basal ganglia dysfunction\textsuperscript{20,35,69,76,77} and are therefore misdiagnosed as having some form of dementia.

Other conditions mimicking the corticobasal syndrome

The typical syndrome characterized by a combination of unilateral movement disorder and cortical features was initially thought to be exclusive to CBD, but clinicopathological studies have shown that only about half of cases with clinical CBS have CBD pathology.1,35,68. Other conditions reported as causing CBS include PSP, AD, Pick disease, tau-negative FTLD, FTDP-17, Creutzfeldt-Jakob disease and LBD.31,60. Given such pathological heterogeneity, CBS should not be considered a hallmark of CBD.
Typical pathology of CBD

Macroscopically, CBD pathology is characterized by asymmetric fronto-parietal cortical atrophy, most severe in the peri-Rolandic distribution. Histological changes include neuronal loss in the affected cortical areas, substantia nigra, globus pallidus and neostriatum along with spongiosis of the cortical neuropil. Tau-positive inclusions (4R isoform) are found in the neurons and glia of both gray and white matter. Intraneuronal inclusions in the substantia nigra and subcortical nuclei resemble the globose neurofibrillary tangles seen in PSP, whereas cortical neuronal inclusions can be diffuse, granular, crescent-shaped or globular, sometimes reminiscent of Pick bodies. Oligodendrogial inclusions (“coiled body”) are widely distributed, along with tau-positive neuropl put threads. The most characteristic lesion seen in CBD is the astrocytic plaque found in affected cerebral cortices; it is considered the pathological hallmark of the disease. Cortical ballooned neurons resembling Pick’s cells are also an important histologic feature. In CBD, there are no tufted astrocytes, which are considered typical of PSP.

Atypical pathology of CBD

As described above, the majority of patients with CBD pathology have predominant involvement of frontoparietal cortices, especially around the central sulcus, associated with some subcortical changes. However, atypical distributions of pathological lesions suggestive of CBD have been reported and can be divided in three subtypes: predominant anterior frontal, superior temporal or subcortical pathology. Some cases have been described where the focus of degeneration was shifted from the central region to the anterior frontal cortex. Interestingly, these patients presented clinically with personality changes, behavioural changes or cognitive decline and not with extrapyramidal features. Another subgroup of patients presenting with progressive aphasia exhibit severe involvement of the superior temporal gyrus or Broca’s area. The term “minimal change CBD” has been used to describe cases of CBD with only minimal cortical pathology and heavier subcortical lesions. Once again, patients with this atypical distribution of lesions do not present with CBS but rather with symmetric parkinsonism poorly responsive to levodopa and prominent gait disturbance, sometimes associated with SNGP and dementia. Therefore, it appears that atypical clinical presentations of CBD are related to unusual distribution of CBD pathological lesions.

Frontotemporal lobar degeneration

Clinical elements

The clinical diagnosis of FTLD refers to a spectrum of clinical syndromes characterized by progressive behavioral changes and language deficits. In 1998, a consensus conference divided the FTLD group into three clinical presentations, now referred to as the behavioral variant of frontotemporal dementia (bv-FTD), progressive non-fluent aphasia (PNFA) and semantic dementia (SD). These three syndromes have overlapping features, typically sharing a combination of behaviour and personality changes, executive dysfunction and language impairment. However, each variant is characterized by the predominant feature. Hence, bv-FTD is diagnosed when cognitive decline and personality changes overshadow the language deficit, and a diagnosis of PNFA or SD is made when language impairment is the predominant symptom. Extrapyramidal features develop in about 30% of patients during the course of the disease, according to Kertesz and Munoz, mostly with the PNFA variant.

Behavioral variant of frontotemporal dementia

Behavioral variant of frontotemporal dementia is characterized by insidious onset and gradual progression of prominent behavior and personality changes associated with frontal executive deficits. Diagnostic criteria include decline in social conduct, poor hygiene, loss of insight, emotional blunting, mental rigidity, impersistence, hyperorality (such as sweet cravings), perseveration and stereotyped behavior. Impulsivity, disinhibition, and apathy are also common. The cognitive profile is notable for executive deficits with relatively spared memory and visuospatial functions. Speech and language can be affected in a similar fashion to that seen in PNFA or SD, although it is not usually a major feature and can occur later. Over time, some patients will develop extrapyramidal elements, such as parkinsonism or CBS.

Progressive Non-Fluent Aphasia

Effortful, non fluent speech with agrammatism is the hallmark of PNFA. Such a language disorder is often associated with apraxia of speech, which is not a language but a speech disorder, characterized by slow speech, abnormal prosody, decreased articulatory accuracy and distorted sound substitutions, additions or repetitions. Similarly to the other FTLD variants, the symptoms of PNFA are insidious and slowly progressive. Although behavioral and personality changes can occur (at onset or up to many years later), such features are not as common as seen in bv-FTD and SD.

Later development of extrapyramidal features, however, is particularly frequent in cases presenting with PNFA and/or apraxia of speech. Corticobasal syndrome is by far the most common motor syndrome associated with primary progressive aphasia, occurring in 40% of patients in one study. Mild parkinsonism or a PSP-like picture have also been reported.

Semantic Dementia

Semantic dementia is characterized by loss of verbal semantic knowledge, impaired comprehension and semantic paraphasias. This entity will not be discussed in detail in this review as it is rarely associated with tau-positive inclusions and has little overlap with CBD and PSP.

Pathology and clinicopathological correlation

Frontotemporal lobar degeneration is a clinical diagnosis associated with heterogeneous pathological entities, which can be divided into tau-positive or tau-negative. The Work Group on Frontotemporal Dementia and Pick’s Disease further classified FTLD into five neuropathological categories (Table 3). Although half the cases of clinical FTLD are tau-negative, it is evident from this classification that CBD and PSP are also possible aetiologies for this clinical presentation. One study...
found CBD pathology to be particularly common, accounting for 20% of their patients with FTLD presentation. Histopathology is difficult to predict in patients with clinical bv-FTD. The majority are found to have tau-negative pathologies such as DLDH, TDP-43 proteinopathy or AD. However, 40-50% of cases will have a tauopathy, most commonly Pick disease but also CBD and PSP. One of the observed trends is that presence of extrapyramidal features at any stage during the disease process more likely predicts tau-positive inclusions.

As opposed to bv-FTD, primary progressive aphasia is highly predictive of an underlying tauopathy, found in about 80% of cases in most studies. Corticobasal degeneration pathology is more likely when parkinsonism or apraxia is present, although many patients never develop such features. Progressive non fluent aphasia has been associated strongly both with Pick’s disease and CBD, whereas PSP typically underlies early and prominent apraxia of speech.

Given the strong clinical and pathological overlap between tau-positive bv-FTD, PNFA, CBD and PSP, some authors argue they should all be considered as subtypes of Pick disease, and the term “Pick complex” was suggested to encompass those disorders.

### Frontotemporal dementia with parkinsonism linked to chromosome 17

Frontotemporal dementia with parkinsonism linked to chromosome 17 is a term used for a heterogeneous group of disorders sharing similar clinical, pathological and genetic features. The clinical phenotype is dominated by dementia of the frontal type or Alzheimer type, associated with variable parkinsonism ranging from a non dopa-responsive parkinsonism (without or without tremor), to a CBS or PSP-like syndrome. All cases of FTDP-17 are caused by a mutation in the gene that encodes microtubule-associated tau (MAPT) on chromosome 17. Most are transmitted in an autosomal dominant fashion, but autosomal recessive transmission has also been described.

### Clinical and pathological overlap

PSP, CBD, PNFA and some cases of bv-FTD and FTDP-17 have overlapping clinical and pathological features. The margins among the clinical presentations of these disorders are blurring, as symptoms thought to be typical for a particular disease can also be found in another disease. For example, PNFA or behavioral and cognitive changes suggestive of bv-FTD are found in CBD or PSP, sometimes with little or absent parkinsonism, CBS can be a prominent feature in PSP or some forms of FTLD, and a PSP-like presentation can be caused by CBD pathology. The clinical overlap is so great that it becomes difficult to predict pathology from the clinical presentation, with a success rate as low as 50% for CBS and 60% for PSP.

Clinicopathological studies in case reports of patients with unexpected clinical presentations for a particular disorder often have microscopic findings that extend beyond the expected areas for this disorder. Severe cortical involvement or asymmetric cortical atrophy expected in CBD is unusual for PSP, but has been described in many cases, most of which exhibited focal cortical signs such as apraxia or aphasia. On the other hand, several cases of CDB presenting with symmetric parkinsonism and prominent gait disturbance have been reported to show minimal cortical pathology. Patients with prominent behavioral changes tend to have more severe pathology in the anterior frontal cortices, and those with progressive aphasia show a high burden of lesions in the dominant temporal lobe. Therefore, it appears the distribution of lesions explains the clinical presentation, and not the morphology of tau aggregates (astrocytic plaque, tufted astrocytes, etc.).

The pathological similarities between CBD and PSP extend beyond the simple topography of tau-inclusions. In both disorders, insoluble tau is predominantly of 4R-tau isoforms consisting biochemically of two major bands at 64 and 68 kDa and a variable minor band at 72 kDa. In both diseases, the tangles are ultrastructurally composed of characteristic 15nm-wide straight tubules. Also, a few studies have failed

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### Table 3: Neuropathological classification of FTLD

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 3R tau-positive inclusions (Pick disease, FTDP-17)</td>
<td></td>
</tr>
<tr>
<td>2. 4R tau-positive inclusions (CBD, PSP, FTDP-17)</td>
<td></td>
</tr>
<tr>
<td>3. 3R and 4R tau-positive inclusions (neurofibrillary tangle dementia, FTDP-17)</td>
<td></td>
</tr>
<tr>
<td>4. Ubiquitin inclusions, most commonly TDP-43 positive (with or without motor neuron disease)</td>
<td></td>
</tr>
<tr>
<td>5. Without tau or ubiquitin inclusions (dementia lacking distinct histopathological features)</td>
<td></td>
</tr>
</tbody>
</table>

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to reveal a clear difference in the tau epitopes displayed by the pathological accumulation of tau in PSP and CBD\(^{107,108}\). Despite the identical composition of tau isoforms, Arai et al showed distinctive patterns of tau fragments on immunoblot analysis of sarkosyl-insoluble brain extracts of patients with CBD and PSP, suggesting that different proteolytic processing of abnormal tau takes place in these two diseases\(^{109,110}\). Another important difference between tau aggregates in PSP and CBD is obviously their morphology: in PSP, the typical tau inclusions take the form of tufted astrocytes, whereas in CBD they form astrocytic plaques. The pathophysiological processes leading to such morphologies are not clear.

It is not known whether PSP and CBD come from distinct insults and pathophysiological processes or if they share some elements of pathophysiology that may evolve differently in different individuals, due to genetic or environmental factors. The latter hypothesis is supported by the report of a single family with histopathologically confirmed CBD in one sibling and PSP in another (both with clinical CBS), along with three more siblings fulfilling the criteria for clinically probable PSP\(^{111}\). However, genetic studies did not reveal a pathogenic tau mutation in this family\(^{111}\) and therefore it is possible that combination of PSP and CBD be related to two different disease processes. Descriptions of combined occurrence of astrocytic plaques and tufted astrocytes in a same patient also suggest a shared pathophysiological pathway for PSP and CBD\(^{112-114}\).

**Genetics**

Recent genetic discoveries also support the overlap between PSP, CBD and some forms of tau-positive FTLD. There have been many reports of mutations of the MAPT gene on chromosome 17 (FTDP-17) resulting in clinical or pathological phenotype suggesting either of these disorders\(^{93-102,115}\). Moreover, the same mutation can result in one clinical syndrome in one family and another in a different family. There is even a report of an identical tau mutation in a family leading to clinical CBS in the son and FTLD in the father\(^{99}\). These evidences reinforce that an identical initial insult (in this case a tau mutation) can lead to distinct clinical and pathological features in the spectrum of PSP, CBD or FTLD in different individuals, suggesting there may be a different processing of the abnormal protein in different subjects which would account for these differences. These differences in the morphology and location of tau aggregates could be related to individual genetic polymorphisms or mutations in the tau gene or other related genes, or to environmental factors which are yet to be identified.

Progressive supranuclear palsy and corticobasal degeneration also share a similar genetic background. Case control studies have demonstrated a significant association between the H1 haplotype of the tau gene and both PSP and CBD\(^{116,117}\). Conrad et al provided the first evidence of an association between the A0 allele of the tau gene and sporadic PSP\(^{118}\); the A0 allele was later shown to segregate with a tau haplotype, designated H1\(^{117}\). In a normal caucasian population, homozygosity for the H1 haplotype (H1/H1) is found in 50–70% of the population, whereas the frequency of H1/H1 in both PSP and CBD is significantly higher (80–90%) compared with controls\(^{115,116,119}\). The exact mechanism by which the H1 haplotype confers an increased risk for these conditions is not known\(^{111}\). One study also reports an association between the A0 allele and FTLD\(^{120}\), whereas others do not support such an association\(^{119,121}\).

**No clinical syndrome is exclusive to tauopathies**

Neurodegenerative diseases not involving tau aggregates but involving deposition of ubiquitin, alphasynuclein or other abnormal proteins can also lead to clinical syndromes suggestive of PNFA, bv-FTD, PSP or CBD. For example, progranulin mutation has been reported in 5–10% of FTLD\(^7\) and can also cause CBS\(^{60}\). Mutations in presenilin, VCP, CHMP2B, TARDP and FUS can also result in a clinical presentation suggestive of FTLD\(^7,122,123\). Alphasynucleinopathies (MSA and LBD), TDP-43 proteinopathies and prion diseases have been clinically mistaken for PSP, CBD or FTLD\(^7,31,41,42,60\). This data emphasizes that no clinical syndrome is exclusive to tauopathies, as other pathophysiological mechanisms can lead to similar symptoms. It can therefore be very difficult to reach a correct clinical diagnosis without pathological confirmation.

**Conclusion**

The clinical presentations suggestive of PNFA, bv-FTD, PSP or CBD do not reliably predict the underlying pathology, as there is considerable overlap between these clinical and pathological syndromes. In particular, bv-FTD and PNFA, although not always associated with tau-positive inclusions, can be presentations of 4R-tauopathies like CBD and PSP. A PSP-like syndrome or CBS can be caused by either PSP, CBD or other tau-positive FTLD. It appears that similarities in clinical features arise from similarities in distribution of tau pathology, despite different types of tau aggregates. Furthermore, there are molecular and genetic evidences that support common pathophysiological roots for PSP and CBD.

Despite obvious overlapping features, there is not enough evidence to conclude that neurodegenerative tauopathies, or even 4R-tauopathies like PSP and CBD, are one single disease. Instead, we feel they should be viewed as part of the same disease spectrum. Future molecular research may reveal that all diseases with predominant tau deposition, even AD, arise from a single disease process which is influenced by genetic and environmental factors, leading to different clinical and pathological expressions. Hopefully, research focusing on pathophysiology of different tauopathies will lead to development of an anti-tau therapy, which could prove useful in treating patients with PSP, CBD, PNFA, FTLD and maybe even AD.

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