REVIEW ARTICLE

Tauopathies: One Disease or Many?

Manon Bouchard, Oksana Suchowersky

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 tau-positive 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 supra nucléaire progressive, la dégénérescence corticobasale et certaines formes de dégénérescence lobaire frontotemporales 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 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[1] (Table 1). 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 sytem lesions, whereas in other conditions like Alzeimer 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 dysfunction1 (Table 1).

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[2-4]. This protein is involved in stabilization and assembly of microtubules[5]. 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[6]. 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 (Figure 1)[7]. 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[6]. 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 (Table 1).

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.

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Table 1: Most prevalent tauopathies. (Modified from Williams, Intern Med J 2006)

	Pattern of dementia	Movement disorder	3R:4R
Predominantly tau pathology			
PSP	Frontal dysexecutive, PNFA	Axial rigidity with postural instability and ophthalmoplegia or asymmetric parkinsonism	1:2-4
CBD	Parietal, frontal dysexecutive, PNFA	Asymmetric parkinsonism, dystonia, myoclonus or tremor, alien limb	1:2
Argyrophilic grain disease	Limbic dementia	No	1:2
Pick disease	Frontal dysexecutive, PNFA, SD	Rare	3:1
FTDP-17	Frontal behavioural or amnestic	Variable parkinsonism, can be PSP-like or CBD-like	1:2, 1:1 or 2:1
Post encephalitic parkinsonism	Rare	Symmetric rigidity with bradykinesia, ophthalmoplegia	1:1
Parkinsonism-dementia complex of Guam	Frontal dysexecutive, cortical	Symmetric rigidity with bradykinesia, ophthalmoplegia	1:1
Guadeloupean parkinsonism	Frontal dysexecutive	Symmetric rigidity with bradykinesia, ophthalmoplegia	1:2
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[8]. 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[9], without tremor or limb bradykinesia and rigidity[10]. 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[11]. 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[12-14]. 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[10,15]. Many recent reports have shown that not only dysarthria, but also non fluent aphasia and apraxia of speech were common in PSP[16]. Neuropsychiatric symptoms develop in more than half the patients within two years of disease onset[17] 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[17-20]. Following symptom onset, patients with PSP experience a relentless progression with death within five to eight years[10].

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[11], we now know that many patients with this condition never develop eye movement abnormalities[14,21-24]. Some individuals present with asymmetric rigidity, tremor and a moderate response to levodopa mimicking idiopathic Parkinson disease (PD)[10,25] or with asymmetrical cortical symptoms mimicking CBD, such as apraxia, alien limb, arm levitation or hemidystonia[21,26-31]. Cognitive decline and behavioural changes are the presenting complaint in 15% to 30% of cases[17,25,32] and can remain the only clinical feature throughout the disease[23,33-35]. Many case reports and series describe patients with an ultimate pathological diagnosis of PSP presenting with isolated apraxia of

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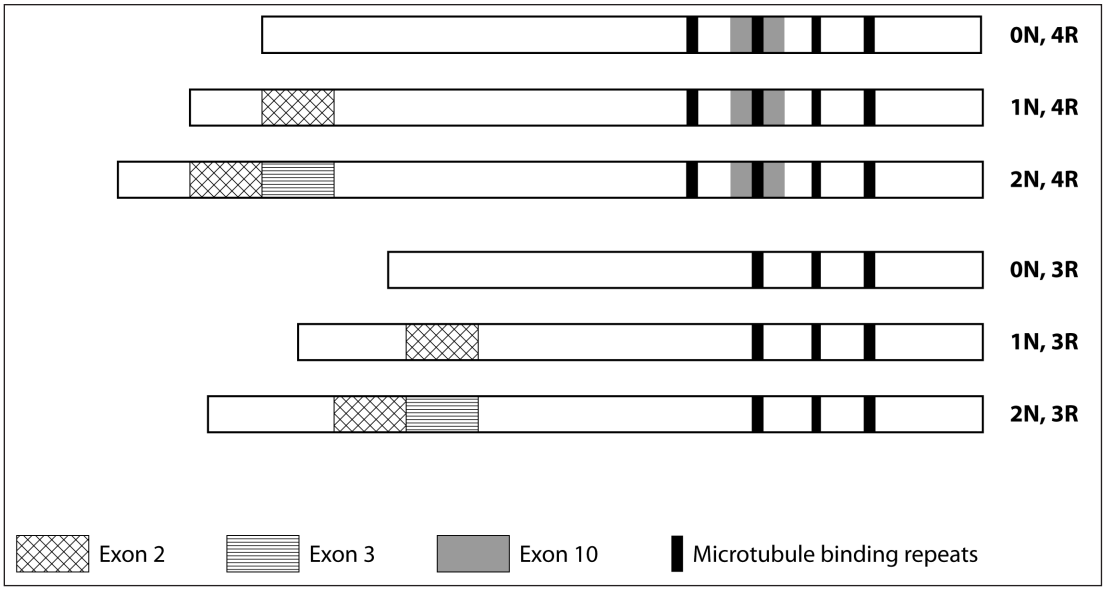

Figure: *Splicing of the different tau isoforms*

speech or progressive non fluent aphasia[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[34-36].

Williams et al[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 levodopa 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[21,24,34,35]. Alternate clinical diagnosis include CBD, PD, primary progressive aphasia, FTLD, AD and cerebrovascular disease[21,24,34,35].

Other conditions mimicking the PSP syndrome

A number of neurodegenerative conditions can mimick 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[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[29,35,41-44].

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

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

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

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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 to 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[10]; 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[24,36,49-53]. 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[10,54,55]. 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[59,62] 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)[71,72]. Progressive aphasia or apraxia of speech are particularly common presenting features[16,73-76] 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[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[31,35,68]. 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.

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Typical pathology of CBD

Macroscopically, CBD pathology is characterized by asymmetric fronto-parietal cortical atrophy, most severe in the peri-Rolandic distribution[49]. Histological changes include neuronal loss in the affected cortical areas, substantia nigra, globus pallidus and neostriatum along with spongiosis of the cortical neuropil[49,78]. 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[49,78]. Oligodendroglial inclusions ("coiled body") are widely distributed, along with tau-positive neuropil threads[78]. The most characteristic lesion seen in CBD is the astrocytic plaque found in affected cerebral cortices[49]; it is considered the pathological hallmark of the disease. Cortical ballooned neurons resembling Pick's cells are also an important histologic feature[49]. 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[49]. Interestingly, these patients presented clinically with personality changes, behavioural changes or cognitive decline and not with extrapyramidal features[51,79,80]. Another subgroup of patients presenting with progressive aphasia exhibit severe involvement of the superior temporal gyrus or Broca's area[51,80]. 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 levo-dopa and prominent gait disturbance, sometimes associated with SNGP and dementia[49,51,80-84]. 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)[85]. These three syndromes have overlapping features, typically sharing a combination of behaviour and personality changes, executive dysfuntion 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[7]. Extrapyramidal features develop in about 30% of patients during the course of the disease, according to Kertesz and Munoz[66], 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[85]. 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[37,38,69,86-88].

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[16]. 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[7].

Later developement 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, occuring in 40% of patients in one study[37]. Mild parkinsonism or a PSP-like picture have also been reported[16].

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)[89]. Although half the cases of clinical FTLD are tau-negative[70,90], it is evident from this classification that CBD and PSP are also possible aetiologies for this clinical presentation. One study

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Table 3: Neuropathological classification of FTLD

1. 3R tau-positive inclusions (Pick disease, FTDP-17)
2. 4R tau-positive inclusions (CBD, PSP, FTDP-17)
3. 3R and 4R tau-positive inclusions (neurofibrillary tangle dementia, FTDP-17)
4. Ubiquitin inclusions, most commonly TDP-43 positive (with or without motor neuron disease)
5. Without tau or ubiquitin inclusions (dementia lacking distinct histopathological features)

found CBD pathology to be particularly common, accounting for 20% of their patients with FTLD presentation[90].

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[35,37,70]. One of the observed trends is that presence of extrapyramidal features at any stage during the disease process more likely predicts tau-positive inclusions[37,63,70,90].

As opposed to bv-FTD, primary progressive aphasia is highly predictive of an underlying tauopathy, found in about 80% of cases in most studies[35,70,91]. Corticobasal degeneration pathology is more likely when parkinsonism or apraxia is present[63,70], although many patients never develop such features. Progressive non fluent aphasia has been associated strongly both with Pick's disease[70] and CBD[37,91], whereas PSP typically underlies early and prominent apraxia of speech[36,91].

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[35,92].

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[45,93-101]. Therefore, FTDP-17 is often misdiagnosed as FTLD, PSP or CBD. Histopathology can resemble that of PSP, CBD or even Pick's disease[101,102]. 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[99]. Many different mutations have been reported, including missense mutations affecting one of the exons (exon 9, exon 10, exon 12, or exon 13), silent mutations affecting exon 10, and substitutions in the intron following exon 10 or more rarely exon 9[78]. All mutations result in formation of hyperphosphorylated tau filaments, which composition (3R or 4R) depends on the type of mutation; mutations in exon 10 or intron 10 will result in 4R-tau accumulation[7,78,94,97].

Are PSP, CBD and FTLD part of the same disease spectrum?

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[35,43].

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[21,26-31]. On the other hand, several cases of CDB presenting with symmetric parkinsonism and prominent gait disturbance have been reported to show minimal cortical pathology[49]. 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[78,103-105]. In both diseases, the tangles are ultrastructurally composed of characteristic 15nm-wide straight tubules[81,106]. Also, a few studies have failed

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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[34,112-114].

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[95]. 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, homozygosy 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 predominent 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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References

1. Williams DR. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. Intern Med J. 2006;36(10):652-60.
2. Gu Y, Oyama F, Ihara Y. Tau is widely expressed in rat tissues. J Neurochem. 1996;67(3):1235-44.
3. Müller R, Heinrich M, Heck S, Blohm D, Richter-Landsberg C. Expression of microtubule-associated proteins MAP2 and tau in cultured rat brain oligodendrocytes. Cell Tissue Res. 1997;288 (2):239-49.
4. Couchie D, Charrière-Bertrand C, Nunez J. Expression of the mRNA for tau proteins during brain development and in cultured neurons and astroglial cells. J Neurochem. 1988;50(6):1894-9.
5. Hirokawa N. Microtubule organization and dynamics dependent on microtubule-associated proteins. Curr Opin Cell Biol. 1994;6(1): 74-81.
6. van Herpen E, Rosso SM, Serverijnen L, et al. Variable phenotypic expression and extensive tau pathology in two families with the novel tau mutation L315R. Ann Neurol. 2003;54(5):573-81.
7. Josephs K. Frontotemporal dementia and related disorders: deciphering the enigma. Ann Neurol. 2008;64(1):4-14.
8. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet. 1999;354(9192):1771-5.
9. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol. 1964;10:333-59.
10. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol. 2009;8(3):270-9.
11. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996;47(1):1-9.
12. Rivaud-Péchoux S, Vidailhet M, Gallouedec G, et al. Longitudinal ocular motor study in corticobasal degeneration and progressive supranuclear palsy. Neurology. 2000;54(5):1029-32.
13. Vidailhet M, Rivaud S, Gouider-Khouja N, et al. Eye movements in parkinsonian syndromes. Ann Neurol. 1994;35(4):420-6.
14. Litvan I, Grimes DA, Lang AE, et al. Clinical features differentiating patients with postmortem confirmed progressive supranuclear palsy and corticobasal degeneration. Neurology. 1999;246 Suppl II:1-5.
15. Scaravilli T, Tolosa E, Ferrer I. Progressive supranuclear palsy and corticobasal degeneration: lumping versus splitting. Mov. Disord. 2005;20 Suppl 1:S21-8.
16. Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. Curr Opin Neurol. 2008;21(6): 688-92.
17. Kaat LD, Boon AJ, Kamphorst W, et al. Frontal presentation in progressive supranuclear palsy. Neurology. 2007;69(8):723-9.
18. Maher E, Smith E, Lees A. Cognitive deficits in the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). J Neurol Neurosurg Psychiatry. 1985:Dec;48(12):1234-9.
19. Grafman J, Litvan I, Gomez C, Chase TN. Frontal lobe function in progressive supranuclear palsy. Arch Neurol. 1990;47(5):553-8.
20. Kertesz A, McMonagle P. Behavior and cognition in corticobasal degeneration and progressive supranuclear palsy. J Neurol Sci. 2010;289(1-2):138-43.
21. Birdi S, Rajput A, Fenton M, et al. Progressive supranuclear palsy diagnosis and confounding features: report on 16 autopsied cases. Mov Disord. 2002 Nov;17(6):1255-64.
22. Dubas F, Gray F, Escourolle R. Steele-Richardson-Olszewski disease without ophthalmoplegia. 6 clinico-anatomic cases. Rev Neurol (Paris). 1983;139(6-7):407-16.
23. Davis P, Bergeron C, McLachlan D. Atypical presentation of progressive supranuclear palsy. Ann Neurol. 1985 Apr;17(4): 337-43.
24. Daniel SE, de Bruin VM, Lees AJ. The clinical and pathological spectrum of Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy): a reappraisal. Brain. 1995;118 (Pt 3:759-70.
25. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005;128(Pt 6):1247-58.
26. Barclay CL, Bergeron C, Lang AE. Arm levitation in progressive supranuclear palsy. Neurology. 1999;52(4):879-82.
27. Oide T, Ohara S, Yazawa M, et al. Progressive supranuclear palsy with asymmetric tau pathology presenting with unilateral limb dystonia. Acta Neuropathol. 2002 Aug;104(2):209-14. Epub 2002 Jun 5.
28. Motoi Y, Takanashi M, Itaya M, et al. Glial localization of four-repeat tau in atypical progressive supranuclear palsy. Neuropathology. 2004;24(1):60-5.
29. Mizuno T, Shiga K, Nakata Y, et al. Discrepancy between clinical and pathological diagnoses of CBD and PSP. J Neurol. 2005;252 (6):687-97.
30. Barclay CL, Lang AE. Dystonia in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1997;62(4):352-6.
31. Boeve BF, Maraganore DM, Parisi JE, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology. 1999;53(4):795-800.
32. Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology. 2003;60(6):910-6.
33. Masliah E, Hansen L, Quijada S, et al. Late onset dementia with argyrophilic grains and subcortical tangles or atypical progressive supranuclear palsy? Ann Neurol. 1991 Apr;29(4): 389-96.
34. Keith-Rokosh J, Ang LC. Progressive supranuclear palsy: a review of co-existing neurodegeneration. Can J Neurol Sci. 2008;35(5): 602-8.
35. Josephs KA, Petersen RC, Knopman DS, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology. 2006;66(1):41-8.
36. Josephs K, Boeve BF, Duffy JR, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. Neurocase. 2005;11(4):283-96.
37. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain. 2005;128(Pt 9):1996-2005.
38. Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. Ann Neurol. 2006;59(1):156-65.
39. Mochizuki A, Ueda Y, Komatsuzaki Y, et al. Progressive supranuclear palsy presenting with primary progressive aphasia--clinicopathological report of an autopsy case. Acta Neuropathol. 2003 Jun;105(6):610-4. Epub 2003 Apr 1.
40. Boeve B, Dickson D, Duffy J, et al. Progressive nonfluent aphasia and subsequent aphasic dementia associated with atypical progressive supranuclear palsy pathology. Eur Neurol. 2003;49 (2):72-8.
41. Josephs KA, Dickson DW. Diagnostic accuracy of progressive supranuclear palsy in the Society for Progressive Supranuclear Palsy brain bank. Mov Disord. 2003;18(9):1018-26.
42. Osaki Y, Ben-Shlomo Y, Lees AJ, et al. Accuracy of clinical diagnosis of progressive supranuclear palsy. Mov Disord. 2004; 19(2):181-9.
43. Gearing M, Olson D, Watts R, Mirra S. Progressive supranuclear palsy: neuropathologic and clinical heterogeneity. Neurology. 1994 Jun;44(6):1015-24.
44. Shiozawa M, Fukutani Y, Sasaki K, et al. Corticobasal degeneration: an autopsy case clinically diagnosed as progressive supranuclear palsy. Clin Neuropathol. 2000 Jul-Aug;19(4):192-9.
45. Ludolph AC, Kassubek J, Landwehrmeyer BG, et al. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. Eur J Neurol. 2009; 16(3):297-309.

46. Hauw J, Daniel S, Dickson D, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology. 1994 Nov;44(11):2015-9.
47. Feany M, Mattiace L, Dickson D. Neuropathologic overlap of progressive supranuclear palsy, Pick's disease and corticobasal degeneration. J Neuropathol Exp Neurol. 1996 Jan;55(1):53-67.
48. Litvan I, Hauw JJ, Bartko JJ, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol. 1996;55(1):97-105.
49. Wakabayashi K, Takahashi H. Pathological heterogeneity in progressive supranuclear palsy and corticobasal degeneration. Neuropathology. 2004 Mar;24(1):79-86.
50. Cordato N, Halliday G, McCann H, et al. Corticobasal syndrome with tau pathology. Mov Disord. 2001 Jul;16(4):656-67.
51. Bergeron C, Pollanen MS, Weyer L, Lang AE. Cortical degeneration in progressive supranuclear palsy. A comparison with cortical-basal ganglionic degeneration. J Neuropathol Exp Neurol. 1997;56(6):726-34.
52. Tsuboi Y, Josephs KA, Boeve BF, et al. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. Mov Disord. 2005;20(8):982-8.
53. Ikebe S, Mori H, Sumino S, et al. A 77-year-old man with gait and gaze disturbance. Nō to Shinkei. 2000;52(3):269-79.
54. Williams DR, Holton JL, Strand C, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain. 2007;130(Pt 6):1566-76.
55. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord. 2007;22(15): 2235-41.
56. Jellinger K. Different tau pathology pattern in two clinical phenotypes of progressive supranuclear palsy. Neurodegener Dis. 2008;5(6):339-46. Epub 2008 Mar 18.
57. Rebeiz JJ, Kolodny EH, Richardson EP. Corticodentatonigral degeneration with neuronal achromasia. Arch Neurol. 1968;18 (1):20-33.
58. Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. Brain. 1989;112 (Pt 5):1171-92.
59. Wenning GK, Litvan I, Jankovic J, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. J Neurol Neurosurg Psychiatry. 1998;64(2):184-9.
60. Wadia P, Lang A. The many faces of corticobasal degeneration. Parkinsonism Relat Disord. 2007;13 Suppl 3:S336-40.
61. Lang A, Riley D, Bergeron C. Cortical-basal ganglionic degeneration. In: Clane DB, editor. Neurodegenerative diseases. Philadelphia: WB Saunders; 1994:877-94.
62. Grimes DA, Lang AE, Bergeron CB. Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology. 1999;53(9):1969-74.
63. Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology. 2000;55(9): 1368-75.
64. Pillon B, Blin J, Vidailhet M, et al. The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology. 1995 Aug;45(8):1477-83.
65. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000;55(11):1621-6.
66. Kertesz A, Munoz D. Relationship between frontotemporal dementia and corticobasal degeneration/progressive supranuclear palsy. Dement Geriatr Cogn Disord. 2004;17(4):282-6.
67. Blake M, Duffy J, Boeve B, Ahlskog E, Maraganore D. Speech and language disorders associated with corticobasal degeneration. J Med Speech Lang Pathol 2003;11:131-46.
68. McMonagle P, Blair M, Kertesz A. Corticobasal degeneration and progressive aphasia. Neurology. 2006;67(8):1444-51.
69. Grimes DA, Lang AE, Bergeron CB. Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology. 1999;53(9):1969-.
70. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol. 2004;56(3): 399-406.
71. Renner J, Burns J, Hou C, et al. Progressive posterior cortical dysfunction: a clinicopathologic series. Neurology. 2004 Oct 12; 63(7):1175-80.
72. Tang-Wai D, Graff-Radford N, Boeve B, et al. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology. 2004 Oct 12;63(7):1168-74.
73. Ikeda K, Akiyama H, Iritani S, et al. Corticobasal degeneration with primary progressive aphasia and accentuated cortical lesion in superior temporal gyrus: case report and review. Acta Neuropathol. 1996;92(5):534-9.
74. Sakurai Y, Hashida H, Uesugi H, et al. A clinical profile of corticobasal degeneration presenting as primary progressive aphasia. Eur Neurol. 1996;36(3):134-7.
75. Bergeron C, Pollanen MS, Weyer L, Black SE, Lang AE. Unusual clinical presentations of cortical-basal ganglionic degeneration. Ann Neurol. 1996;40(6):893-900.
76. Mimura M, Oda T, Tsuchiya K, et al. Corticobasal degeneration presenting with nonfluent primary progressive aphasia: a clinicopathological study. J Neurol Sci. 2001 Jan 15;183(1): 19-26.
77. Mathuranath PS, Xuereb JH, Bak T, Hodges JR. Corticobasal ganglionic degeneration and/or frontotemporal dementia? A report of two overlap cases and review of literature. J Neurol Neurosurg Psychiatry. 2000;68(3):304-12.
78. Revesz T, Holton JL. Anatamopathological spectrum of tauopathies. Mov Disord. 2003;18 Suppl 6:S13-20.
79. Tsuchiya K, Ikeda K, Uchihara T, Oda T, Shimada H. Distribution of cerebral cortical lesions in corticobasal degeneration: a clinicopathological study of five autopsy cases in Japan. Acta Neuropathol. 1997;94(5):416-24.
80. Ikeda K. Basic pathology of corticobasal degeneration. Neuropathology 1997;17:127-33.
81. Wakabayashi K, Oyanagi K, Makifuchi T, et al. Corticobasal degeneration: etiopathological significance of the cytoskeletal alterations. Acta Neuropathol. 1994;87(6):545-53.
82. Su M, Yoshida Y, Hirata Y, Satoh Y. An autopsy case of corticobasal degeneration associated with atrophy of pons and cerebellum. Niigata Medical J. 1999;113:350-1.
83. Ohara S, Tsuyuzaki J, Oide T, et al. A clinical and neuropathological study of an unusual case of sporadic tauopathy. A variant of corticobasal degeneration? Neurosci Lett. 2002;330(1):84-8.
84. Hattori M, Yoshida M, Ojika K, et al. An autopsy case of corticobasal degeneration without prominent cortical pathology--an imitator of progressive supranuclear palsy. Rinshō Shinkeigaku. 2000;40(4):372-7.
85. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51(6):1546-54.
86. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry. 1994;57(4):416-8.
87. Schneider J, Watts R, Gearing M, Brewer R, Mirra S. Corticobasal degeneration: neuropathologic and clinical heterogeneity. Neurology. 1997 Apr;48(4):959-69.
88. Rinne JO, Lee MS, Thompson PD, Marsden CD. Corticobasal degeneration. A clinical study of 36 cases. Brain. 1994;117 (Pt 5: 1183-96.
89. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol. 2001;58(11):1803-9.
90. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. Ann Neurol. 2006;59(6): 952-62.

91. Josephs K, Duffy J, Strand E, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain. 2006 Jun;129(Pt 6):1385-98.
92. Kertesz A, Davidson W, Munoz DG. Clinical and pathological overlap between frontotemporal dementia, primary progressive aphasia and corticobasal degeneration: the Pick complex. Dement Geriatr Cogn Disord. 1999;10 Suppl 1:46-9.
93. Dumanchin C, Camuzat A, Campion D, et al. Segregation of a missense mutation in the microtubule-associated protein tau gene with familial frontotemporal dementia and parkinsonism. Hum Mol Genet. 1998;7(11):1825-9.
94. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998;393(6686):702-5.
95. Bugiani O, Murrell JR, Giaccone G, et al. Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. J Neuropathol Exp Neurol. 1999;58(6):667-77.
96. Soliveri P, Rossi G, Monza D, et al. A case of dementia parkinsonism resembling progressive supranuclear palsy due to mutation in the tau protein gene. Arch Neurol. 2003;60(10): 1454-6.
97. Rademakers R, Cruts M, van Broeckhoven C. The role of tau (MAPT) in frontotemporal dementia and related tauopathies. Human Mutation. 2004;24(4):277-95.
98. Ferrer I, Pastor P, Rey MJ, et al. Tau phosphorylation and kinase activation in familial tauopathy linked to deln296 mutation. Neuropathol Appl Neurobiol. 2003;29(1):23-34.
99. Pastor P, Pastor E, Carnero C, et al. Familial atypical progressive supranuclear palsy associated with homozigosity for the delN296 mutation in the tau gene. Ann Neurol. 2001;49(2): 263-7.
100. Rossi G, Marelli C, Farina L, et al. The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. Mov Disord. 2008 Apr 30;23(6):892-5.
101. Stanford P, Halliday G, Brooks W, et al. Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: expansion of the disease phenotype caused by tau gene mutations. Brain. 2000 May;123 (Pt 5):880-93.
102. Bird TD, Nochlin D, Poorkaj P, et al. A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). Brain. 1999;122 (Pt 4:741-56.
103. Ksiezak-Reding H, Morgan K, Mattiace LA, et al. Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration. Am J Pathol. 1994;145(6):1496-508.
104. Buée Scherrer V, Hof PR, Buée L, et al. Hyperphosphorylated tau proteins differentiate corticobasal degeneration and Pick's disease. Acta Neuropathol. 1996;91(4):351-9.
105. Buée L, Delacourte A. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick's disease. Brain Pathol. 1999;9(4):681-93.
106. Tellez-Nagel I, Wiśniewski H. Ultrastructure of neurofibrillary tangles in Steele-Richardson-Olszewski syndrome. Arch Neurol. 1973 Nov;29(5):324-7.
107. Arai T, Ikeda K, Akiyama H, et al. Different immunoreactivities of the microtubule-binding region of tau and its molecular basis in brains from patients with Alzheimer's disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. Acta Neuropathol. 2003;105(5):489-98.
108. Berry RW, Sweet AP, Clark FA, et al. Tau epitope display in progressive supranuclear palsy and corticobasal degeneration. J Neurocytol. 2004;33(3):287-95.
109. Arai T, Ikeda K, Akiyama H, et al. Intracellular processing of aggregated tau differs between corticobasal degeneration and progressive supranuclear palsy. Neuroreport. 2001;12(5):935-8.
110. Arai T, Ikeda K, Akiyama H, et al. Identification of amino-terminally cleaved tau fragments that distinguish progressive supranuclear palsy from corticobasal degeneration. Ann Neurol. 2004;55(1):72-9.
111. Tuite PJ, Clark HB, Bergeron C, et al. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. Arch Neurol. 2005;62 (9):1453-7.
112. Li F, Iseki E, Kosaka K, et al. Progressive supranuclear palsy with fronto-temporal atrophy and various tau-positive abnormal structures. Clin Neuropathol. 1996 Nov-Dec;15(6):319-23.
113. Katsuse O, Iseki E, Arai T, et al. 4-repeat tauopathy sharing pathological and biochemical features of corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathol. 2003;106(3):251-60.
114. Tan C, Piao Y, Kakita A, et al. Frontotemporal dementia with co-occurrence of astrocytic plaques and tufted astrocytes, and severe degeneration of the cerebral white matter: a variant of corticobasal degeneration? Acta Neuropathol. 2005;109(3): 329-38.
115. Di Maria E, Tabaton M, Vigo T, et al. Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. Ann Neurol. 2000 Mar;47(3):374-7.
116. Houlden H, Baker M, Morris HR, et al. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. Neurology. 2001;56(12):1702-6.
117. Baker M, Litvan I, Houlden H, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Mol Genet. 1999;8(4):711-5.
118. Conrad C, Andreadis A, Trojanowski J, et al. Genetic evidence for the involvement of tau in progressive supranuclear palsy. Ann Neurol. 1997 Feb;41(2):277-81.
119. Morris HR, Janssen JC, Bandmann O, et al. The tau gene A0 polymorphism in progressive supranuclear palsy and related neurodegenerative diseases. J Neurol Neurosurg Psychiatry. 1999;66(5):665-7.
120. Hughes A, Mann D, Pickering-Brown S. Tau haplotype frequency in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Exp Neurol. 2003;181(1):12-6.
121. Panegyres PK, Zafiris-Toufexis K. Polymorphisms in the tau gene in sporadic frontotemporal dementia and other neuro-degenerative disorders. Eur J Neurol. 2002;9(5):485-9.
122. Gallo M, Tomaino C, Puccio G, et al. Novel MAPT Val75Ala mutation and PSEN2 Arg62Hys in two siblings with frontotemporal dementia. Neurol Sci. 2010;31(1):65-70.
123. Seelaar H, Rohrer JD, Pijnenburg YAL, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry. 2011 May;82(5):476-86. Epub 2010 Oct 22.