alzheimer's research&therapy

REVIEW

Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias

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Abstract

Microtubule-associated protein tau encoded by the *MAPT* gene binds to microtubules and is important for maintaining neuronal morphology and function. Alternative splicing of *MAPT* pre-mRNA generates six major tau isoforms in the adult central nervous system resulting in tau proteins with three or four microtubule-binding repeat domains. In a group of neurodegenerative disorders called tauopathies, tau becomes aberrantly hyperphosphorylated and dissociates from microtubules, resulting in a progressive accumulation of intracellular tau aggregates. The spectrum of sporadic frontotemporal lobar degeneration associated with tau pathology includes progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. Alzheimer's disease is considered the most prevalent tauopathy. This review is divided into two broad sections. In the first section we discuss the molecular classification of sporadic tauopathies, with a focus on describing clinicopathologic relationships. In the second section we discuss the neuroimaging methodologies that are available for measuring tau pathology (directly using tau positron emission tomography ligands) and tau-mediated neuronal injury (magnetic resonance imaging and fluorodeoxyglucose positron emission tomography). Both sections have detailed descriptions of the following neurodegenerative dementias – Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease.

Background

Molecular classification of tauopathies

Neurodegeneration is the progressive loss of selective populations of vulnerable neurons. Research efforts investigating sporadic and familial neurodegenerative diseases have identified distinct clinicopathologic relationships related to the accumulation of hallmark brain lesions found in selectively vulnerable neuroanatomical distributions. Neurodegeneration can thus be classified by clinical presentation, anatomic distribution, or molecular mechanisms (that is, specific proteinopathies). Strong evidence supports a pathogenic role of altered microtubule-associated protein tau (MAPT) as the shared molecular mechanism of disease amongst the collectively termed tauopathies. Although tauopathies share a common molecular mechanism, the selective vulnerability of anatomic systems and clinical presentations significantly varies across disease types. Moreover, the inclusions and cell types involved can range from neuronal cells to glial cells. Based on the predominance of disorders involving tau neuropathology, it is recognized as the most commonly associated misfolded protein in human neurodegenerative diseases (Table 1).

Hyperphosphorylation of tau is thought to destabilize the microtubule-associated proteins, which act as stabilizers of microtubule networks. The degree of phosphorylation regulates the physiological functions of tau, thus effecting microtubule interaction and intracellular trafficking [1]. Abnormal accumulation of hyperphosphorylated tau that makes up neurofibrillary tangles (NFTs), composed of paired helical filaments (PHFs) and straight filaments, is found in Alzheimer's disease (AD) brains (Table 2). In addition, there are several non-AD tauopathies with focal cortical neuronal loss and gliosis that fit into the spectrum of sporadic frontotemporal lobar degeneration with tau pathology (FTLD-tau), including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease (PiD). Table 1 provides a more extensive list of neurodegenerative diseases with tau inclusions – including, but not limited to, argyrophilic grains disease [2], Parkinsonism–dementia complex of Guam [3], and white matter tauopathy with globular glial inclusions [4-9].

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Table 1 Neurodegenerative diseases with tau inclusions

Pathologic diagnosis	Histologic tau findings
Alzheimer's disease	Neurofibrillary tangles (NFTs) found in neocortex and limbic regions. Intracellular NFTs are found to be both 3R and 4R tau-positive with a preferential shift to 3R immunoreactivity in extracellular NFTs.
Amyotrophic lateral sclerosis of Guam	NFTs positive for 3R and 4R found in neocortex and limbic areas with a predilection for cortical layers II and II.
Argyrophilic grain disease	Spindle-shaped, 4R tau-positive lesions accumulate in neuronal processes. Grains are typically found in the neuropil of limbic areas, but can be found diffusely deposited in cortex. Coiled bodies in oligodendrocytes and tau-positive pretangles can be abundantly found.
Chronic traumatic encephalopathy	Widespread NFTs, tau-immunoreactive astrocytic inclusions, and neuritic pathology can be found with a predilection for superficial cortical layers and sulcal depths. Irregular, patchy tau pathology observed in cortex.
Corticobasal degeneration	4R tau-positive ballooned neurons, astrocytic plaques, and neuropil threads are found in both gray and white matter of cortical and striatal regions.
Diffuse neurofibrillary tangles with calcification	NFTs and neuropil threads found diffusely deposited in frontal and temporal cortex, as well as limbic areas.
Down's syndrome	NFTs and granulovaculoar degeneration can be found in the hippocampus.
Familial British dementia	NFTs and neuropil threads found relatively restricted to limbic regions.
Familial Danish dementia	NFTs and neuropil threads found in limbic with abnormal neurites limited to amyloid-laden blood vessels and variable involvement of cortical regions.
Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations)	Widespread neuronal and glial cytoplasmic inclusions immunopositive for 3R, 3+4R, or 4R tau. Morphology of lesions varies with reportedly observed coiled bodies, tufted astrocytes, and astrocytic plaques.
Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations)	NFT pathology can be found in a similar Alzheimer's-like limbic and cortical distribution.
Gerstmann–Sträussler–Scheinker disease	Tau pathology can be absent, not reported, or inconsistently reported as widespread neurofibrillary pathology depending on the PRNP mutation.
Guadeloupean parkinsonism	Widespread neurofibrillary pathology can be found as NFTs, neuropil threads, and astrocytic tufts.
Myotonic dystrophy	NFTs in limbic and brainstem regions.
Neurodegeneration with brain iron accumulation	Diffuse neuritic pathology in cortex, but rare NFT pathology.
Niemann–Pick disease, type C	NFTs, neuropil threads, and oligodendroglial coiled bodies range from transentorhinal confinement to widespread limbic and cortical involvement.
Non-Guamanian motor neuron disease with neurofibrillary tangles	NFTs can be found in limbic structures, midbrain, and pontine nuclei.
Parkinsonism–dementia complex of Guam	NFTs positive for 3R and 4R found in cortical areas with a predilection for cortical layers II and III. Tau pathology is also found in limbic, basal ganglia, brainstem, and spinal cord. Granular hazy tau inclusions are found in motor cortex, amygdala, and inferior olivary nucleus.
Pick's disease	Widespread spherical cytoplasmic 3R tau-positive inclusions (Pick bodies) can be found in hippocampus, basal ganglia, brainstem nuclei, and especially cortex.
Postencephalitic parkinsonism	Widespread tau-positive neuronal and glial lesions. Globose NFTs are a prominent feature in brainstem nuclei, especially substantia nigra and locus coeruleus. NFTs are more common in limbic structures than cortex, and have a predilection for layers II and III.
Progressive supranuclear palsy	4R tau-positive globose NFTs, tufted astrocytes, and coiled bodies are often found in the subthalamic nucleus, globus pallidus, ventral thalamus, cerebellar dentate nucleus, and variable involvement of cortex.
SLC9A6-related mental retardation	Glial tau pathology, resembling coiled bodies, can be found in brainstem and cerebellar white matter tracts. Astrocytic plaques can also be found in brainstem, thalamus, and cerebral white matter. NFT-like inclusions can be found in brainstem and thalamic nuclei, hippocampus, and cortex.
Subacute sclerosing panencephalitis	Glial fibrillary tangles can be found in oligodendroglia. NFTs can be found differentially distributed in hippocampus and/or cerebral cortex.
Tangle predominant dementia	4R predominant NFT accumulation relatively combined to limbic regions.
White matter tauopathy with globular glial inclusions	Widespread globular oliogdendroglial inclusions, less so in astroglial, immunoreactive for 4R-tau.

Table 2 Biochemical and ultrastructural characteristics of Alzheimer's disease and frontotemporal lobar degeneration tauopathies

	Tau repeat	Filaments (width)	Periodicity	Reference
AD	3R ≈ 4R	PHF (10 to 20 nm) >> SF (~15 nm)	80 nm	[6]
PSP	4R >3R	SF (15 nm); rare twisted filament (15 to 30 nm)	>100 nm	[7]
CBD	4R >3R	SF >> twisted filament (15 to 30 nm)	160 nm	[8]
PiD	3R >4R	SF (15 nm) >> twisted filament (15 to 30 nm)	160 nm	[9]

Abbreviations: AD – Alzheimer's disease; PSP - progressive supranuclear palsy; CBD - corticobasal degeneration; PiD - Pick's disease; PHF - paired helical filament; SF – straight filament; nm - nanometer

This brief review summarizes the clinicopathologic patterns and neuroimaging signatures of sporadic AD and FTLD-tau. Over the past 15 years, knowledge about the genetics of familial FTLD research has exploded – yielding the discoveries of mutations in the gene for *MAPT* [10-12], mutations in the gene encoding progranulin (*GRN*) [13,14], and recently the abnormal hexanucleotide repeat expansion in the gene *C9ORF72* [15,16]. Readers are referred to recent reviews that cover the breadth of genetic forms of AD [17] and FTLD [18].

Clinicopathologic patterns of sporadic Alzheimer's disease and FTLD-tau

Heterogeneity of tau neuropathology is the consequence of alternative splice forms and post-translational modifications (for example, phosphorylation, ubiquitination, and acetylation) [19]. Six isoforms of the tau protein are expressed in the human brain, which results from alternatively spliced pre-mRNA [20,21]. Alternative splicing of exon 2, exon 3, and exon 10 of *MAPT* affects the number of microtubule-binding repeats. Dependent upon the alternative splicing of exon 10, the tau species will contain three or four repeat domains (3R and 4R, respectively). Preferential accumulation of 3R or 4R tau can be found in various tauopathies, revealing a nonuniform biochemical pattern (Table 2) [22-25]. PSP and CBD brains have predominantly 4R tau pathology and are considered 4R tauopathies (4R > 3R), whereas PiD is considered a 3R tauopathy (3R > 4R). In AD the 3R:4R tau ratio is close to one and is thus not referred as a 3R or 4R tauopathy. The recent revision of FTLD neuropathologic diagnostic criteria takes into account molecular genetics, biochemistry characteristics, and current immunohistochemical techniques [26].

AD is a progressive neurodegenerative disorder and is the most common form of dementia in the aging population. Intracellular tau NFTs and extracellular amyloid-beta (Aβ) plaques are the histopathologic hallmarks of AD (Figure 1a,b,c) [27]. AD patients typically present initially with memory impairment, correlating with tau NFTs in medial temporal lobe structures including the entorhinal cortex, amygdala, and cornu ammonis field 1/subiculum of the hippocampus early in the disease process [28,29]. The stereotypic progression from medial temporal lobe structures to association cortices and eventual involvement of primary cortices was originally described by Braak and Braak [28]. Dementia associated with AD pathology has an insidious onset with progressive worsening of cognition. Patients can have an amnestic presentation or can have nonamnestic presentations including language, visuospatial, and executive dysfunction that are probably due to atypical patterns of AD neuropathology [30-32]. The recently updated clinical diagnostic criterion for dementia associated with AD pathology incorporates imaging and cerebrospinal fluid biomarkers in efforts to improve earlier detection and tracking of disease progression [33,34].

In AD, hyperphosphorylated, insoluble aggregates composed of 3R and 4R tau develop into NFTs and neuritic plaques (Aβ extracellular lesions surrounded by tau neuropil threads and dystrophic neurites) [20,35,36]. Updated AD neuropathologic diagnostic criteria implement an ABC standardized scoring scheme [37] that includes modified versions of Thal phasing for Aβ plaques (A) [38], the Braak and Braak NFT stage (B) [28,39], and a neuritic plaque score defined by the Consortium to Establish a Registry for Alzheimer's Disease (C) [40]. These criteria have the advantage of ensuring uniformity in neuropathologic assessment of AD across research institutions to improve clinicopathologic studies, and in particular highlight the occurrence of AD pathology in the absence of cognitive impairment, which may represent a preclinical phase of AD [41].

PSP is a sporadic neurodegenerative disorder with prominent hyperphosphorylated tau aggregates in the brain accompanied by neuronal loss and gliosis. In general, the anatomical distribution of tau pathology correlates with the clinical presentation of PSP patients, with the basal ganglia, substantia nigra, and subthalamic nucleus being the most affected brain regions [42]. PSP can often be diagnosed on macroscopic examination by the presence of midbrain atrophy with dilation of the cerebral aqueduct, superior cerebellar peduncle and subthalamic nucleus atrophy [43], and variable cortical involvement of the peri-Rolandic cortex [44]. Microscopically, PSP neuropathology is characterized by neuronal inclusions called globose NFTs, tufted astrocytes [45], and tau immunoreactive inclusions in

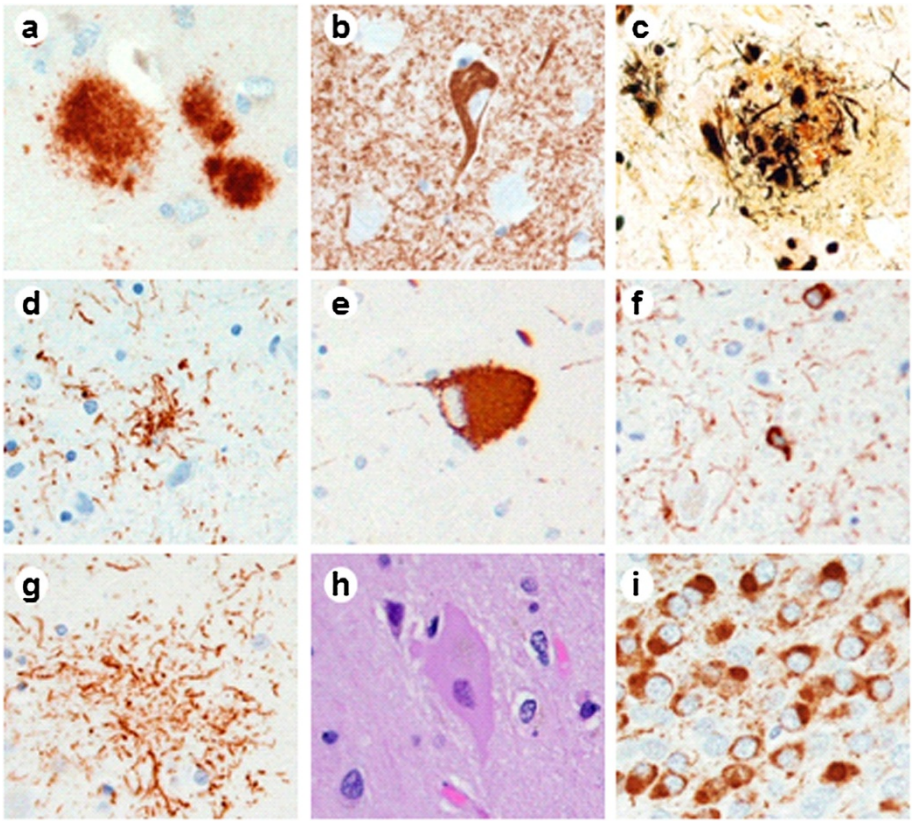

Figure 1 Neuropathologic inclusions seen in tauopathies range from intracellular to extracellular and from neuron to glia. Alzheimer's disease neuropathologic inclusions used to classify severity based on an ABC scoring scheme include **(a)** extracellular amyloid-beta (Aβ) plaque (33.1.1 antibody), **(b)** neurofibrillary tangle (NFT) composed of abnormal tau fibrils (paired helical filament phosphorylated tau antibody), and **(c)** Aβ deposits surrounded by dystrophic neurites produce neuritic plaques (observed with Bielschowsky silver stain). Tau immunohistochemistry in progressive supranuclear palsy shows abnormal tau aggregates in **(d)** astrocytes called tufts or tufted astrocytes, **(e)** neurons called globose NFTs, and **(f)** oligodendrocytes termed coiled bodies. Tau-immunoreactivity in corticobasal degeneration (CBD) shows abnormal tau aggregates in **(g)** astrocytes called astrocytic plaques and tau-immunoreactive threads in the gray and white matter in neocortical and subcortical regions and **(h)** swollen, achromatic or ballooned neurons (hematoxylin and eosin). **(i)** Tau-immunoreactive, dense spherical neuronal cytoplasmic inclusions called Pick bodies are observed in granular neurons of the dentate fascia in Pick's disease. (a), (b), (c) Medial temporal cortex. (d), (e), (f), (g), (i) Phospho-tau antibody CP13. (d), (f) Red nucleus at the level of the oculomotor nerve. (e) Substantia nigra. (g), (h) Mid-frontal cortex.

oligodendrocytes, termed coiled bodies (Figure 1d,e,f). There is often marked neuronal loss and gliosis in the subthalamic nucleus, globus pallidus, ventral thalamus, and cerebellar dentate nucleus. Ultrastructural characterization of tau pathology in PSP reveals mostly straight filaments, with only rare twisted filaments having been observed (Figure 2 and Table 2).

The large majority of PSP patients present with Richardson syndrome, also known as PSP syndrome, characterized by postural instability leading to unexplained backward falls within the first year of symptom onset, axial rigidity, dysarthria, dysphagia, progressive vertical ophthalmoplegia, personality changes, and bradykinesia that is unresponsive to levodopa. Although this description comprises the typical PSP cases, there is a great deal of pathologic heterogeneity that causes patients to present with various clinical syndromes. Atypical variants of PSP include frontotemporal dementia (FTD) [46], nonfluent/agrammatic primary progressive aphasia and apraxia of speech [47], and pure akinesia with gait freezing syndrome due to severe pallido-nigro-luysial degeneration [48,49]. The cause of this extensive variability associated with PSP is currently unknown, but underlying genetic variation is expected to play a role.

Although there are rare familial cases, CBD and PSP are considered sporadic disorders. Yet, despite their sporadic nature, genetic variants on the H1 major haplotype harboring the *MAPT* locus that spans ~1.8 Mb of DNA on chromosome 17q21 are a strong genetic risk factor for CBD and PSP [50-55]. Recent progress in our understanding of PSP genetics is credited to the completion of the first, of its kind, PSP genome-wide association study [56], and future studies aim to use common genetic variation

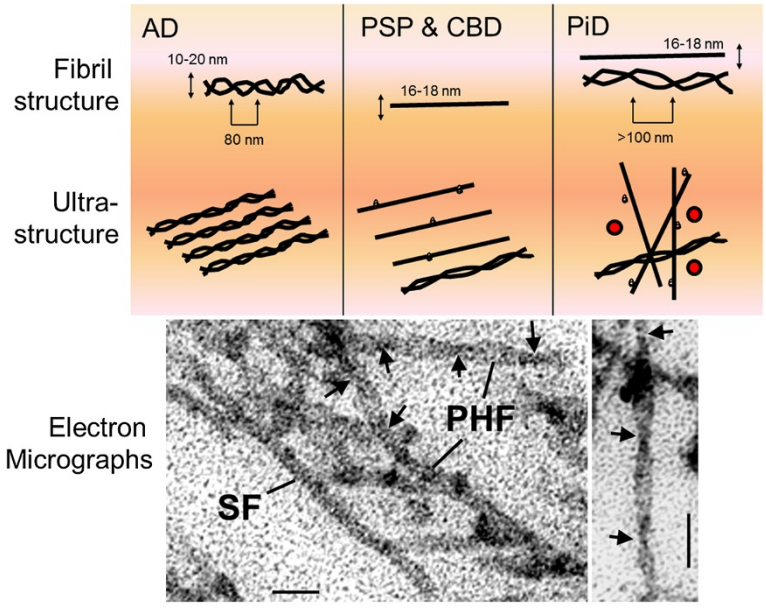

Figure 2 Ultrastructural characterization of tau filaments in Alzheimer's disease and frontotemporal lobar degeneration tau. (Top, left) Alzheimer's disease (AD) tau fibrils form paired helical filaments typically observed in flame-shaped cytoplasmic inclusion. (Top, middle) Progressive supranuclear palsy (PSP) tau fibrils typically form straight filaments with rare twisted filaments, similar to corticobasal degeneration (CBD), that aggregate in less compact bundles associated with dense granular material. (Top, right) Pick's disease (PiD) tau fibrils are mainly straight filaments with some loosely twisted wide filaments that aggregate in close proximity and can be associated with dense granular material. (Bottom, left) Electron micrograph of tau filaments from AD showing paired helical filaments (PHF) and straight filament (SF). Bar, 50 nm. (Bottom, right) Twisted filaments in PSP, CBD and PiD have longer periodicity. Bar, 100 nm. Arrows point at twists of filaments.

within PSP to determine whether they associate with and influence variability in tau neuropathology.

CBD is a rare neurodegenerative disorder classified as a 4R tauopathy due to neuronal and glial aggregates of hyperphosphorylated tau in both gray and white matter of the neocortex, basal ganglia, thalamus, and, to a lesser extent, the brainstem of these patients [57]. The hallmark glial lesion in CBD is the astrocytic plaque (Figure 1g), which is not observed in other disorders [58,59]. Microscopic inspection of the affected cortices often shows cortical thinning with neuronal loss, gliosis and many ballooned neurons (Figure 1h). Ultrastructural characterization of tau pathology in CBD reveals mostly straight filaments with some wide twisted filaments having been observed (Figure 2 and Table 2). CBD was first described as a distinct clinicopathologic entity in the 1960s by Rebeiz and coworkers [60] and has some overlapping clinical and pathologic features with PSP, yet is considered a distinct disease entity [61,62]. CBD is associated with focal cortical atrophy and, because of this, patients can present with a wide range of clinical syndromes depending on the location of the highest tau burden pathology and marked cortical atrophy that can be observed on imaging using voxel-based morphometric analysis (reviewed in [63]). Because CBD pathology can cause multiple different neurologic syndromes, defining clinical diagnostic criteria for CBD has been extremely challenging [64-67]. CBD patients can present with corticobasal syndrome [68-70], PSP syndrome [70-73], FTD [71,74-76], or nonfluent/agrammatic primary progressive aphasia [77,78]. CBD patients presenting with corticobasal syndrome often have asymmetric atrophy of the superior frontal cortex, whereas those patients presenting with PSP syndrome have symmetric atrophy slightly more anterior than corticobasal syndrome patients and have greater hindbrain involvement (that is, brainstem and cerebellum) [72,73,79].

PiD is a rare form of FTLD-tau that is associated with severe circumscribed cortical atrophy of the frontal and temporal lobes, described as knife-edge atrophy of cortical gyri. Patients suffering from PiD will have clinical syndromes corresponding to the location of the most affected cortical regions, most often presenting with behavioral variant FTD [80], nonfluent/agrammatic primary progressive aphasia with peri-Sylvian atrophy [81,82], an amnestic syndrome [80], upper motor neuron signs due to pyramidal tract degeneration [83], or progressive limb apraxia due to frontoparietal atrophy [84,85]. Familial forms of PiD are extremely rare and are due to *MAPT* mutations p.G272V [86] and p.G389R [87,88]. The histopathologic inclusions observed in PiD, termed Pick bodies, are round intraneuronal inclusions composed of hyperphosphorylated 3R tau [89,90] and are argyrophilic on Bielschowsky but are Gallyas-

negative (PiD neuropathology reviewed in [91]). Hippocampal pyramidal neurons and granular neurons of the dentate fascia are particularly susceptible to Pick bodies (Figure 1i). There is diffuse spongiosis in affected cortical regions and ballooned achromatic neurons (Pick cells) in middle and lower cortical layers, and variable tau-immunoreactive glial inclusions [26]. Ultrastructural characterization of tau pathology in PiD also reveals mostly straight filaments, with some wide twisted filaments having been observed (Figure 2 and Table 2).

Imaging tauopathies in neurodegenerative diseases

In vivo imaging of molecular processes and pathologies has evolved significantly in the last two decades. Imaging surrogates of pathology are especially useful in the neurodegenerative dementias where there is no clear one-to-one correspondence between the neuropathologic findings at autopsy and the clinical expression of the disease in each subject. There are two noninvasive imaging technologies that are used widely to measure tau pathology and/or tau-mediated injury in the brain – positron emission tomography (PET) and magnetic resonance imaging (MRI).

PET imaging involves injecting a radioactive tracer into a subject intravenously. After the tracer is chemically incorporated into a biologically active molecule of interest, the tracer decays and annihilates to produce gamma rays that are measured using the PET cameras. The typical radioactive tracers use carbon-11, oxygen-15 and fluorine-18 (^{18}F) isotopes. The most commonly used PET tracer is fluorodeoxyglucose (FDG; ^{18}F agent), which is a glucose analog used to measure glucose uptake in the organ of interest. On the other hand, MRI is based on the principles of nuclear magnetic resonance of the atomic nuclei. The following section discusses both the tau tracers/ligands that are available for direct measurement of tau using PET imaging as well as MRI and PET imaging methods that indirectly measure tau-mediated neuronal injury. We will also specifically discuss the expected patterns of neurodegeneration seen in different tauopathies in MRI.

Tau ligands in positron emission tomography

In the recent past after the invention of excellent amyloid tracers (such as carbon-11-labeled Pittsburgh compound B and [^{18}F]florbetapir), the search for a tau binding ligand has intensified. The search properties include nontoxicity, ability to cross the blood–brain barrier (that is, low molecular weight lipophilic molecules), rapid clearance from the bloodstream and selective binding to specific targets (that is, tau) in a reversible fashion [92]. Due to the longer half-life of ^{18}F (110 minutes) and a temporal advantage favorable for commercialization and distribution, most of the tau ligands are ^{18}F-based. Below, we summarize the three tau ligands that have shown the most promise and describe their selective potential in AD and FTLD-tau. For a more in-depth review on the pharmacokinetic requirements of tau imaging ligands, the readers are directed to a recent review by Jensen and colleagues [93].

The radiotracer 2-(1-(6-((2-[^{18}F]fluoroethyl) (methyl) amino)-2-naphthyl)ethylidene) malononitrile ([^{18}F]FDDNP) was the first reported PET contrast agent to successfully detect both Aβ deposits and NFTs in brains of AD patients [94,95]. [^{18}F]FDDNP was identified through direct visual inspection of tissue fluorescence in postmortem brain tissue. The putative protein target is the aggregate conformation of β-pleated sheets, thus prompting investigations into the specificity of the radiotracer to AD neuropathology. After observing [^{18}F]FDDNP-labeled prion plaques found in Creutzfeldt–Jakob disease and Gerstmann–Sträussler–Scheinker disease, follow-up studies sought to further characterize the protein deposits potentially labeled by the radiotracer [96]. A subsequent immunofluorescent study demonstrated binding of [^{18}F]FDDNP to similarly labeled Congo red protein deposits, including prion plaques, cerebral amyloid angiopathy, amyloid plaques, NFTs, and Lewy bodies [97]. Pick bodies, globose NFTs, and glial cytoplasmic inclusions were not visualized with [^{18}F]FDDNP, implying the absence of structural conditions necessary to bind the molecule [97]. Contradictory to the lack of fluorescent staining in PSP postmortem tissue described in the aforementioned study, a more recent [^{18}F]FDDNP PET study convincingly demonstrates a higher signal in areas known to be vulnerable to tau pathology in PSP – subcortical gray matter and brainstem structures [98]. Representative images from this study [98] are shown in Figure 3. There is contention, however, whether the tracer concentration used on patients is sufficient to adequately label NFTs and/or other pathologies. A major drawback of [^{18}F]FDDNP is its nonspecific binding to other proteins in addition to tau.

A second group from the Tohoku University in Japan employed a screen of organic compounds targeting β-sheet structures (for example, quinolone, benzoxazole, and benzimidazole) in brain tissue [99]. One of these derivatives was found to bind tau with a higher affinity over Aβ,2-(4-aminophenyl)-6-(2-([^{18}F]fluoroethoxy))quinolone ([^{18}F]THK523) [100,101]. To investigate the binding properties of [^{18}F] THK523, an *in vitro* binding assay using recombinant tau and $A\beta_{1-42}$ fibrils was performed. The overall number of binding sites was ~5-fold higher for tau compared with $A\beta_{1-42}$ [100]. Follow-up immunofluorescence and autoradiography studies in postmortem brain tissue demonstrated specificity to tau tangles in the cortex and hippocampus [100,101]. Although there appears to be white matter retention visible in the autoradiography photomicrographs, the signal relative to the grey matter pathology appeared to

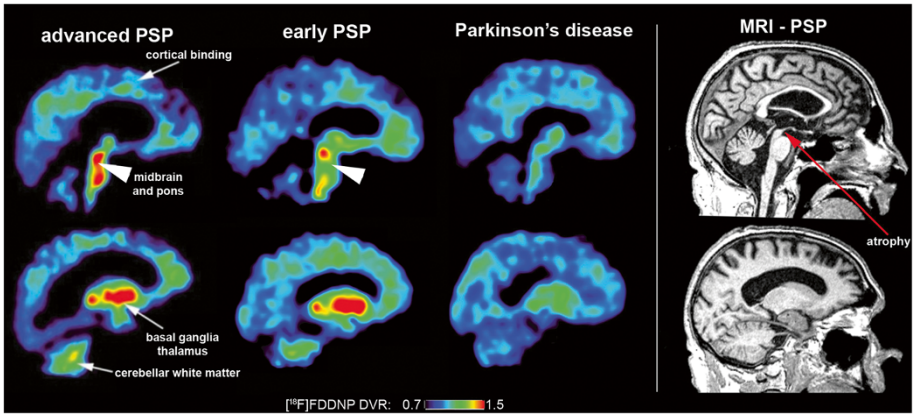

Figure 3 Tau ligand binding patterns in progressive supranuclear palsy. (Left) Typical 2-(1-(6-((2-[^{18}F]fluoroethyl) (methyl)amino)-2-naphthyl) ethylidene) malononitrile ([^{18}F]-FDDNP) binding patterns seen in advanced progressive supranuclear palsy (PSP), early PSP and Parkinson's disease. [^{18}F]-FDDNP signal due to tau binding seen in the basal ganglia, midbrain and pons in PSP subjects but not in Parkinson's disease. (Right) Sagittal magnetic resonance imaging (MRI) scan of a PSP patient with characteristic midbrain atrophy. DVR, distribution volume ratio, a scaled measure that indicates the linear function of radioligand binding. Reprinted with permission from [98].

remain distinguishable. Further supportive evidence for the selectivity of [^{18}F]THK523 as a tau ligand was demonstrated by microPET assessment of the Alzheimer-like tau pathology in the Tg4510 line, which expresses the P301L MAPT mutation. Higher binding was observed compared with that seen in APP/PS1 mice, which expresses the Swedish APP and presinilin-1 transgene (Alzheimer-like amyloid pathology model). Despite evidence of higher cortical retention in AD, a study comparing AD, semantic dementia, and healthy control patients showed no distinct pattern of [^{18}F] THK523 radiotracer retention [102]. More work demonstrating *in vivo* PET images of human tauopathies will be of interest to future clinical use of [^{18}F]THK523 as a tau-directed imaging agent, although preliminary work has been quite promising.

The most recently described tau ligand came from the Siemens' Molecular Imaging Group (recently acquired by Avid/Lily) screening over 900 compounds to determine which had both higher binding affinity and selectivity for tau tangles compared with Aβ plaques [103]. Two compounds, [^{18}F]T807 and [^{18}F]T808, met optimum pharmacokinetic characteristics for tau ligands with >27-fold higher affinity for PHF-tau compared with Aβ, as well as low white matter binding. [^{18}F]T808 reportedly underwent slow defluorination, compared with the metabolically stable [^{18}F]T807 compound. The follow-up study investigating the efficacy of these imaging agents thus focused on [^{18}F]T807 [104]. Autoradiographic evidence of tau selectivity was evident in Aβ-positive/tau-negative brain tissue when compared with Aβ-negative/tau-positive brain tissue [104,105]. Various brain regions were analyzed for the uptake of [^{18}F]T807 across healthy controls, mild cognitive impairment, and AD patients [104]. Healthy controls showed low binding, whereas medial temporal and association cortices demonstrated stereotypic severity expected in AD [28]. The mild cognitive impairment patient was found centered between healthy controls and the AD patients – except in the occipital cortex, which would be expected.

The favorable pharmacokinetics, low white matter binding, and apparent association with cognitive status in AD make [^{18}F]T807 a promising tau ligand for future clinical studies in AD. Given the initial screen for PHF-tau in AD, it will be of interest to observe the efficacy of [^{18}F]T807 as a tau ligand in FTLD tauopathies because they are primarily composed of straight filaments. Twisted filaments found in CBD and PiD have a wider periodicity (~160 nm) compared with AD (~80 nm), which may interfere with tau ligand binding (Table 2). The PHFs in AD are less compact and more of a pure filamentous bundle compared with PiD, which have a compartmentalized combination of straight and twisted filaments mixed with other material – possibly masking the tau epitope. Labeling PSP and CBD may be easier given the more diffuse, shorter filamentous nature of the tau. Past studies evaluating tau epitopes identified in AD and their specificity in PSP [106], CBD [107], and PiD [108] have shown immunopositive labeling despite differences in periodicity.

Another challenge of tau imaging is the abundance of tau aggregates in the white matter of many tauopathies, as discussed by Villemagne and colleagues [109]. Amyloid imaging has faced the issue of high nonspecific binding of amyloid ligands in white matter [110], but binding of tau to white matter may have a biologic or pathologic mechanism of explanation. Tau has been shown to localize to the axon in white matter, with some evidence of localization to the somatodendritic compartment

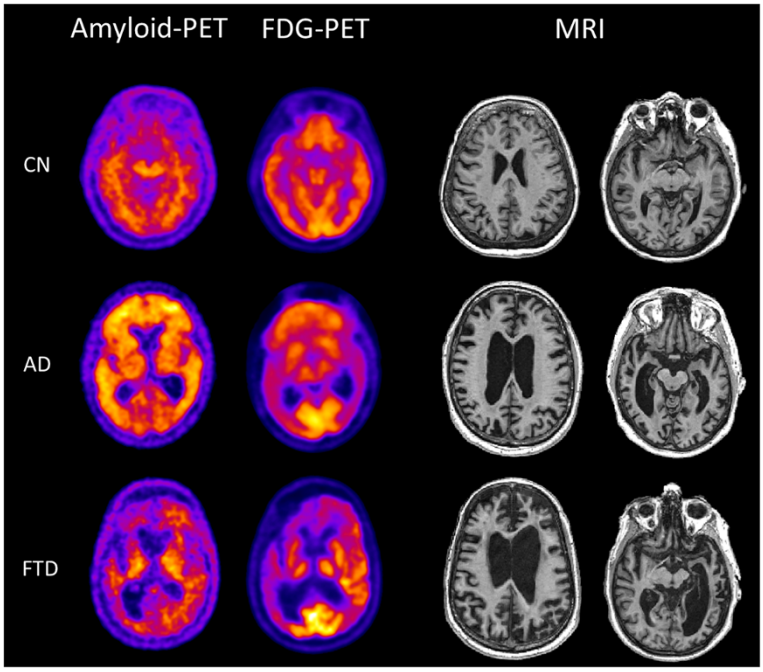

Figure 4 Amyloid imaging of Alzheimer's disease and frontotemporal dementia. Typical amyloid positron emission tomography (Pittsburgh Compound B-PET), fluorodeoxyglucose (FDG)-PET and magnetic resonance imaging (MRI) images seen in a cognitively normal individual (CN), an Alzheimer's disease (AD) patient and a frontotemporal dementia (FTD) patient. The CN individual shows no evidence of amyloid deposition, normal metabolic uptake and normal structural MRI scan. The AD patient shows significant amyloid uptake throughout the brain, significant low parietal lobe FDG uptake and significant ventricular expansion on the MRI scan. The FTD patient shows no significant amyloid deposition, significant frontal and temporal lobe deficits and atrophy, which are both highly asymmetric.

[111,112]. Although tau imaging in AD would favor low white matter binding, specific binding in the white matter would probably benefit the differential diagnosis of CBD and PSP [73] or identify cases of white matter tauopathy with globular glial inclusions [4,5]. In comparison with high specific-to-nonspecific tau binding in the gray matter, the white matter may have an equal ratio or a higher nonspecific-to-specific binding ratio given the reduced blood flow compared with gray matter.

Imaging tau-mediated neuronal injury

Both structural MRI and FDG-PET are used for measuring tau-mediated neuronal injury. Structural MRI measures brain morphometry. MRI captures structural changes that occur on a microscopic level in neurodegenerative disorders: gray matter atrophy related to the loss of neurons, synapses, and dendritic dearborization; white matter atrophy related to loss of structural integrity of white matter tracts, presumably resulting from demyelination and dying back of axonal processes; and *ex vacuo* expansion of cerebrospinal fluid spaces. Strong correlations have been shown between the volume measured on MRI and histology-based neuronal numbers in the hippocampus [113]. Since there is a significant negative correlation between NFT density and neuronal counts [114], MRI has been considered a sensitive marker of tau pathology – although more work is needed to establish the contribution of coexisting neuropathologies (for example, neuritic plaques, TDP-43, ubiquitin). Pathology studies in AD have shown high correlations between structural changes on MRI and Braak NFT stages [28], validating structural MRI as a biomarker for measuring neuron loss associated with NFT burden [115-117]. Emerging MRI modalities such as diffusion tensor imaging and resting-state functional MRI have also shown significant promise in capturing changes due to tau pathology [118,119]. FDG-PET, on the other hand, is used to measure net brain metabolism, although including many neural and glial functions, largely indicating synaptic activity [120,121]. Brain glucose metabolism measured with FDG-PET is highly correlated with postmortem measures of the synaptic structural protein synaptophysin [122].

We now discuss the typical patterns of atrophy seen on MRI and metabolic deficits seen on FDG-PET for each of the major tauopathies – AD, PSP, CBD, and PiD. In AD, atrophy patterns seen on MRI are similar to the progression of NFT pathology discussed earlier. Typical AD begins and is ultimately most severe in the medial temporal lobe, particularly the entorhinal cortex and hippocampus. Later the atrophy is seen in the basal temporal lobe and posterior cingulate gyrus and precuneus.

The visual assessment [123] or the quantification of the hippocampus [124] is the most commonly used biomarker for measuring tau-mediated injury in AD and has been validated using several autopsy studies [125]. FDG-PET patterns in AD show significant hypometabolism in the bilateral posterior cingulate gyri and the parietotemporal area in AD [126].

PSP is characterized by significant atrophy and metabolic changes in the brainstem with additional involvement of cortical regions, specifically the medial frontal regions [127]. Atrophy of the midbrain on mid-sagittal MRI, described as the hummingbird sign, is a useful predictor of PSP [128]. Visual assessment or quantification of atrophy in the superior cerebellar peduncle on MRI significantly increases accuracy of the clinical diagnosis [129].

CBD is characterized by significant focal atrophy and metabolic changes that are typically asymmetric and are observed in the frontoparietal regions with involvement of subcortical structures [130,131]. Additionally, the rates of global atrophy observed in CBD are significantly higher than those in other neurodegenerative disorders [132].

PiD is associated with widespread metabolic abnormality and atrophy in the frontal regions and to a lesser extent in the temporal lobe regions [133,134]. Imaging examples of cognitive normal subjects, FTD subjects, and AD subjects with an amyloid tracer, FDG-PET, and MRI are shown in Figure 4. The use of neuroimaging for identifying neuroanatomical patterns underlying different FTLD clinical syndromes as well as differential prediction of tau pathology from other pathologies underlying FTLD (ubiquitin, progranulin) has been an area of active research [118,134-137].

Conclusions and future directions

The vast heterogeneity of both clinical presentations and molecular neuropathology across the major tauopathies underlies the importance of biomarker development. Given that there is no one-to-one match between the neuropathologic findings at autopsy and the clinical expression of the disease in each subject, *in vivo* MRI and PET imaging that measures tau either directly or indirectly will be extremely useful for identifying the pathologic substrate of the disease. In addition to aiding the early detection and differential diagnosis of the tauopathies in neurodegenerative disorders, *in vivo* imaging measures can play several important roles – predicting the risk of progression in at-risk populations, evaluating disease progression, measuring efficacy of therapeutics, screening for clinical trials, as well as making mechanistic inferences into the disease process. FDG and MRI are currently excellent surrogates for measuring neuronal injury due to tau, but tau imaging will provide clinicians with a direct *in vivo* tool to measure tau pathology. Thorough validation using antemortem autopsy studies, however, is still needed in future analyses.

Note: This article is part of a series on *Tau-based therapeutic strategies*, edited by Leonard Petrucelli. Other articles in this series can be found at http://alzres.com/series/tau_therapeutics.

Abbreviations

[^{18}F]FDDNP: 2-(1-(6-((2-[^{18}F]fluoroethyl) (methyl)amino)-2-naphthyl)ethylidene) malononitrile; [^{18}F]THK523: Aβ,2-(4-aminophenyl)-6-(2-([^{18}F]fluoroethoxy)) quinolone; ^{18}F: Fluorine-18; 3R: Three repeat domain; 4R: Four repeat domain; AD: Alzheimer's disease; Aβ: Amyloid-beta; CBD: Corticobasal degeneration; FDG: Fluorodeoxyglucose; FTD: Frontotemporal dementia; FTLD: Frontotemporal lobar degeneration; MAPT: Microtubule-associated protein tau; MRI: Magnetic resonance imaging; NFT: Neurofibrillary tangle; PET: Positron emission tomography; PHF: Paired helical filament; PiD: Pick's disease; PSP: Progressive supranuclear palsy.

Competing interests

CRJ has no financial activities related to the present article, but financial activities not related to the present article include consultation fees from Pfizer, Johnson & Johnson, Janssen, Eisai, and Elan for consultancies. The remaining authors declare that they have no competing interests.

Acknowledgements

The authors would like to thank Farzan Fatemi for help with creating the imaging figure. The neuropathology figure would not be possible without the technical expertise of Virginia Philips, Linda Rousseau, and Monica Castanedes-Casey and the gifts of CP13 and PHF-1 antibodies from Dr Peter Davies at The Feinstein Institute for Medical Research, Manhasset, NY, USA. This review was supported by National Institutes of Health grants: Mayo Alzheimer Disease Research grant (P50 AG016574), Mayo Clinic Study on Aging (Alzheimer Disease Patient Registry; U01 AG006786), NIH/NINDS Morris K. Udall Center (P50-NS072187), K99-AG37573, R01-AG011378 and R01-AG041851. The authors would also like to thank the CurePSP|Society for Progressive Supranuclear Palsy, The Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation, The Robert E. Jacoby Professorship for Alzheimer's Research, and the Mayo Foundation for Education and Research.

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Published: 02 Jan 2014

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10.1186/alzrt231
Cite this article as: Murray *et al.*: Clinicopathologic assessment and imaging of tauopathies in neurodegenerative dementias. *Alzheimer's Research & Therapy* 2014, 6:1