The tauopathies: Neuroimaging characteristics and emerging experimental therapies

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INTRODUCTION

Tauopathies are a heterogeneous group of neurodegenerative disorders (NDs) in which the primary underlying disease process is intracellular deposition of abnormal tau protein. Diseases often categorized as tauopathies include progressive supranuclear palsy (PSP), chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), and frontotemporal lobar degeneration (FTLD). Many tauopathies vary in their clinical presentation and overlap substantially in presentation, making diagnosis of a specific primary tauopathy difficult. Examples of other less common tauopathies that will not be discussed in this review include frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), argyrophilic grain disease, and aging-related tau astrogliopathy, among several others and are discussed

Abstract

The tauopathies are a heterogeneous group of neurodegenerative disorders in which the prevailing underlying disease process is intracellular deposition of abnormal misfolded tau protein. Diseases often categorized as tauopathies include progressive supranuclear palsy, chronic traumatic encephalopathy, corticobasal degeneration, and frontotemporal lobar degeneration. Tauopathies can be classified through clinical assessment, imaging findings, histologic validation, or molecular biomarkers tied to the underlying disease mechanism. Many tauopathies vary in their clinical presentation and overlap substantially in presentation, making clinical diagnosis of a specific primary tauopathy difficult. Anatomic imaging findings are also rarely specific to a single tauopathy, and when present may not manifest until well after the point at which therapy may be most impactful. Molecular biomarkers hold the most promise for patient care and form a platform upon which emerging diagnostic and therapeutic applications could be developed. One of the most exciting developments utilizing these molecular biomarkers for assessment of tau deposition within the brain is tau-PET imaging utilizing novel ligands that specifically target tau protein. This review will discuss the background, significance, and clinical presentation of each tauopathy with additional attention to the pathologic mechanisms at the protein level. The imaging characteristics will be outlined with select examples of emerging imaging techniques. Finally, current treatment options and emerging therapies will be discussed. This is by no means a comprehensive review of the literature but is instead intended for the practicing radiologist as an overview of a rapidly evolving topic.

KEYWORDS

chronic traumatic encephalopathy, corticobasal degeneration, frontotemporal lobar degeneration, molecular imaging, progressive supranuclear palsy, tau, tauopathies
more comprehensively in other publications.5–7 Additional NDs such as Alzheimer disease (AD) are associated with heterogeneous protein deposition, which includes abnormal deposition of tau; however, this heterogeneity raises controversy as to the true role of tau.8 Therefore, AD will not be discussed in this review except where comparisons are made.

Normal tau is a microtubule-associated protein essential for the stability and formation of microtubules and is predominantly found within axons.9–11 Neuronal bodies, dendrites, astrocytes, and oligodendrocytes have also been observed to contain tau protein.12,13 Tau exists in an unfolded state physiologically; however, it can form aggregates when abnormally hyperphosphorylated.14–16 This hyperphosphorylated state is thought to lead to abnormal interactions with microtubules, resulting in microtubule dysfunction and aggregate formation, a hallmark of primary tauopathies. Recent research suggests that pathologic tau aggregates can induce tau pathology in adjacent cells, resulting in prion-like propagation.17–21

One pitfall of the radiology literature is a potential bias toward classifying NDs based on imaging characteristics, which are rarely specific to a single neurodegenerative disease. While imaging findings can correlate with disease progression, they may not have fully manifested when a given therapy would be most impactful. The point in the disease course at which a patient presents can dramatically influence classification. Additionally, lack of the full clinical picture at the reading station could potentially reduce sensitivity for subtle imaging findings, which may have been best appreciated with specific imaging protocols. A common example is qualitative MRI evaluation of brain atrophy without utilizing quantitative volumetric assessment of subregional brain volumes, which requires specialized software. Atrophy can be subtle early in the disease course, making reliable quantitative assessment difficult until late in the disease course, at which time disease modifying treatments may not be an option. Pathologic/histologic verification remains the gold standard, but biopsy is invasive and prone to complications, and postmortem tissue acquisition after death is not useful to the patient. Autopsy results have shown the clinical diagnoses are often inaccurate.22,23 Tracking symptoms and imaging patterns over time may allow for more accurate diagnosis.

Characterization of the neurodegenerative diseases by underlying molecular mechanism allows for a molecular biomarker approach to classification, facilitating development of more specific and sensitive imaging biomarkers and therapy targets.24 Identifying aberrations years before they clinically manifest allows for early diagnosis and offers targeted therapy options, which include small molecule drugs, antibodies, and cell therapies.

This review is by no means a comprehensive evaluation of the literature and instead is meant for the radiologist as an overview of a rapidly evolving topic. The background, significance, and clinical presentation of each disease will be discussed, highlighting the difficulty in discerning various overlapping diseases (Table 1). The underlying pathologic mechanisms that lead to tauopathies will be outlined at the protein level along with available and emerging imaging techniques.

Finally, current treatment options and emerging therapies will be reviewed.

**PROGRESSIVE SUPRANUCLEAR PALSY**

### Background, significance, and clinical presentation

PSP is a neurodegenerative disease initially described by Richardson in 1963 with the clinical syndrome of supranuclear vertical ophthalmoplegia, pseudobulbar palsy, and dementia.25 The classic presentation of PSP is often referred to as Richardson’s syndrome and consists of dementia, supranuclear vertical ophthalmoplegia, and postural instability with falls.26–29 PSP typically presents in the seventh decade and has a male predilection.26,27 The prevalence of PSP ranges from 5 to 6 cases per 100,000 people in the United States.30 Median survival from disease onset is just under 6 years with pneumonia being the most common cause of death.26,29 While uncommon, PSP can impose a significant economic cost to patients, their caregivers, and society with one study suggesting an annual cost of up to 2.7 million euros in the European Union alone.31

Richardson’s syndrome is the classic clinical presentation of PSP, although significant symptom heterogeneity makes a definitive diagnosis clinically difficult. PSP can present with Parkinsonism and be misdiagnosed as idiopathic Parkinson’s disease (PD).26,27 Clinical features that may help differentiate PSP from PD include vertical supranuclear gaze palsy, early postural instability, falls, rapidly progressive disease, and Parkinsonism with poor response to levodopa.26,28 No specific PSP laboratory tests are clinically available, although studies utilizing the Real-Time Quaking-Induced Conversion (RT-QuIC) assay are showing great promise for distinguishing the various proteinopathies. The test specific to the tauopathies is being referred to as the 4 tau (4T) RT-QuIC assay.32–34 The assay takes advantage of the protein seeding mechanism, amplifying miniscule amounts of the abnormal CSF protein to detectable levels (Figure 1).

### Underlying pathologic mechanism

Neuropathologically, PSP is characterized by neuronal loss and gliosis with deposition of abnormal tau aggregates predominantly within the basal ganglia, subthalamic nucleus, substantia nigra, and pons.26–37 An additional hallmark feature is the presence of tau-positive inclusions within astrocytes, referred to as glial fibrillary tangles or tufted astrocytes.37,38 Macroscopically, PSP is associated with marked volume loss of the midbrain, superior cerebellar peduncle, and subthalamic nucleus with loss of pigment within the substantia nigra.37,38 PSP is classified as a 4R tauopathy due to the fact that the deposited tau aggregates predominantly consist of tau isoforms containing four repeats within the microtubule-binding domain.37,40,41 The anatomic distribution of abnormal tau deposition has been shown to correlate with clinical presentation (Figure 2).
TABLE 1  Tauopathy overview

| Tauopathy | Presentation | Pathology | Tau distribution | PET findings | Lobar atrophy |
|-----------|-------------|-----------|------------------|--------------|---------------|
| PSP       | Supranuclear vertical ophthalmoplegia, pseudobulbar palsy, and dementia, 7th decade, male | Tau-positive inclusions within astrocytes (gliarial fibrillary tangles) | Basal ganglia, substantia nigra, and pons | 18F-FDG hypometabolism in midbrain, posterior frontal lobes, basal ganglia, and thalamus, 18F-THK-5351 tau PET shows promise | Midbrain, superior cerebellar peduncle, subthalamic nuclei (hummingbird sign) |
| CTE       | Personality and behavioral changes, memory loss, and speech and gait difficulty with repetitive trauma history, sixth to seventh decade with some presenting earlier | Hyperphosphorylated tau neurofibrillary tangles predominantly within the superficial cortex | Perivascular distribution along small cortical vessels | Diffusely increased uptake on [18F]AV-1451 PET | Diffuse atrophy and corpus callosum thinning with progressive limbic system involvement |
| CBD       | Progressive, asymmetric apraxia and akinetic-rigid syndrome, fifth-seventh decade | Tau-reactive lesions within neurons and glial cells, astrocytic plaque | Affected contralateral cortex and striatum with astrocytic plaques | 18F-FDG hypometabolism in frontal and parietal cortices, thalami, and caudate nuclei contralateral to clinically affected side. 18F-THK-5351 tau PET shows promise | Parasagittal peri-Rolandic atrophy with superior frontal gyrus involvement contralateral to the clinically affected side |
| FTLD      | Language-related dementia syndromes termed primary progressive aphasia with preserved memory, fifth-seventh decade | Cortical microvacuolation and neuronal loss, predominantly within layer II along with gliosis and myelin loss within the underlying white matter | Spherical deposition hippocampi, basal ganglia, and the superficial neocortical layers of the frontal and temporal lobes | 18F-FDG-PET hypometabolism within the frontal and anterior temporal lobes in a pattern corresponding with the FTLD syndrome. 18F-THK-5351 tau PET shows promise | Frontal and/or temporal lobe atrophy which varies by subtype. Occasional parietal lobe involvement. Sparing of the occipital lobes |

Abbreviations: CBD, corticobasal degeneration; FTLD, frontotemporal lobar degeneration.

Imaging characteristics and emerging imaging techniques

While no imaging features are entirely specific to any one primary tauopathy, certain features suggestive of PSP can be helpful in making the diagnosis. Midbrain atrophy is one of those features, but can also be seen in association with conditions such as PD and CBD. Certain features of the midbrain atrophy may help increase the specificity of anatomic imaging findings. Marked midbrain atrophy resulting in a decreased AP diameter has been referred to as the “hummingbird” sign when viewed in the sagittal plane (Figure 3A). Additionally, the superior surface of the midbrain is typically flat or concave in those with PSP, as compared to convex in healthy patients. Atrophic concavity of the lateral midbrain tegmentum has also been described in PSP, termed the “morning glory” sign (Figure 5). A reduced midbrain-to-pons diameter ratio (below 0.52) measured on midsagittal images has also been found to have sensitivity and specificity in pathologically proven cases of PSP (Figure 3A). Finally, the ratio of the midbrain to pons areas as measured on midsagittal images has been shown to have predictive value for early death from PSP with a cutoff value of 0.12 (Figure 3B).

A more advanced MRI measurement system known as the MR Parkinsonism index (MRPI) has shown to be helpful in differentiating PSP from PD (Figure 4). This technique involves multiple additional measurements, including areas of the pons and midbrains, as well as widths of the superior and middle cerebellar peduncles. The MRPI was later updated to the MRPI 2.0, which incorporated measurements of the third ventricle with improved sensitivity. Automated quantitative techniques such as voxel-based morphometry have shown promise in distinguishing PSP from other tauopathies, as well as potentially tracking volumetric biomarkers of disease progression and/or therapy response. Diffusion tensor imaging has also demonstrated potential utility in differentiating PSP from alpha-synucleinopathies and predicting disease severity.

18F-Fluorodeoxyglucose (18F-FDG) brain PET demonstrates in hypometabolic activity within the midbrain, posterior frontal lobes, basal ganglia, and thalamus in patients with PSP. While these findings are potentially helpful in diagnosing PSP, their absence does not preclude the diagnosis. Dopamine active transporter (DAT) SPECT imaging may reveal decreased striatal binding relative to normal patients; however, this finding is not specific as it may be seen in a host of other neurodegenerative diseases. Beta-amyloid PET imaging, a
FIGURE 1  4 tau real-time quaking-induced conversion (4T RT-QuIC) assay for tauopathy detection. The patient tissue sample with suspected abnormal tau protein is delivered into a solution containing many copies of the normal recombinant tau protein. The solution is placed on a shaker for 1 minute followed by 1 minute of incubation. If abnormal tau protein is present, the normal recombinant tau proteins will become misfolded and propagate the misfolding pattern thus causing a significant amplification. The fluorescent probe will bind only the misfolded proteins and therefore the amplified signal can be detected using a fluorimeter. Normal negative controls do not fluoresce.

There are several limitations to tau-PET imaging with [18F]AV-1451. Some studies have shown no correlation with [18F]AV-1451 uptake and severity of symptoms including motor dysfunction and cognitive impairment. The pattern of tau deposition in PSP may not actually correlate with the pattern of [18F]AV-1451 uptake, although it does correlate with the observed patterns of FDG metabolism. Additionally, some evidence has shown that uptake of [18F]AV-1451 within the basal ganglia increases with age in both control patients and patients with PSP, limiting its utility. Cognitively normal patients have also been shown to have uptake of [18F]AV-1451 in other areas of the brain (referred to as "off-target" binding), further confounding imaging findings.

Due to these limitations, other potential PET agents specific for tau have been investigated, including [18F]-THK5105 and [18F]-THK5117. While these agents were found to show uptake in typical areas of tau deposition primarily in patients with AD, they also had some issues with "off-target" binding, particularly within the subcortical white matter. In order to decrease this nonspecific binding, the chemical structure of [18F]-THK5117 was modified in order to create...
FIGURE 2 Abnormal tau seeding and propagation. The normal tau protein (top) converts to a misfolded tau protein and starts aggregating and altering the conformation of neighboring tau proteins. The larger oligomer unit forms fibrils that then build into disorganized aggregates. The aggregates can spread interneuronally across the synapse to begin the process of destruction in neighboring neurons. Beginning locally in a given part of the brain, the disease spreads to more distant parts of the brain to induce the neurodegenerative disease (shown on the bottom). This is shown progressing from the darker blue color in the brainstem to the lightest blue color in the more distal cortical regions of the cerebrum.

18F-THK-5351 demonstrated higher binding affinity for neurofibrillary tangles and has less white matter binding, making it more sensitive for abnormal tau protein. There is also evidence that 18F-THK-5351 binds to abnormal tau protein within the basal ganglia and brainstem in patients with PSP.

Potential limitations to imaging with 18F-THK-5351 include off-target binding within the basal ganglia, which has been demonstrated to an extent, similar to and possibly greater than that of 18F-JAV-1451. There is also evidence that 18F-THK-5351 may bind to monoamine oxidase B (MAO-B) within the brain in addition to pathologic tau, potentially confounding examinations showing increased uptake of the radiotracer. Further research into these agents is ongoing in order to fully realize their potential in imaging tau deposition in PSP as well as other tauopathies.

CHRONIC TRAUMATIC ENCEPHALOPATHY

Background, significance, and clinical presentation

CTE is a progressive neurodegenerative condition characterized by abnormal deposition of hyperphosphorylated tau protein in patients who have experienced repetitive brain trauma. Patients may include athletes participating in contact sports, military personnel, or others experiencing head trauma. Generally speaking, CTE has been associated with personality and behavioral changes, memory loss, and speech and gait abnormalities. The vast majority of cases studied have occurred in males, although whether this observation is explained by a true male predilection for the disease versus an increased likelihood of male participation in high-impact contact sports such as North American football is not yet clear. The prevalence of CTE is difficult to estimate since it is only diagnosable post-mortem and has unique risk factors. Furthermore, most of the studies attempting to estimate prevalence have focused on athletes rather than the general population, potentially limiting the generalizability of those studies. Current estimates on the prevalence of CTE in football players range from 9.6% up to nearly 100%. While mortality and survival data on patients with CTE are limited due to the condition only recently being more pathologically characterized, it has been estimated that professional North American football players face a threefold neurodegenerative mortality risk. Additionally, a recent study demonstrated an increased risk of death secondary to neurodegenerative disease in a cohort of former soccer players with a hazard ratio >5.

It has been shown that there are two main presentation patterns in patients with CTE: one in relatively younger patients (average age 51) presenting mainly with mood and behavioral disturbances, and one in somewhat older patients (average age 69) presenting mainly with cognitive impairment. The severity of patient symptoms appears to correlate with the number of traumatic brain injuries suffered as well as the duration of the patient’s engagement in the sport/activity. It should be noted that some patients have reported symptoms of CTE as young as 25 years of age.

Underlying pathologic mechanism

On gross pathology, CTE has been classically described as having the following features: diffuse cerebral atrophy, thinning of the corpus callosum, cavum septum pellucidum with fenestrations, enlarged lateral and third ventricles, and cerebellar scarring. Marked atrophy of the hippocampi, amygdala, and entorhinal cortex can be seen within increasing disease severity. Other gross pathological features that may be observed include atrophy of the thalami, mamillary bodies, brainstem, and olfactory bulbs as well as pallor of the substantia nigra and locus ceruleus. Microscopically, CTE typically shows irregular, dense...
FIGURE 3  Hummingbird sign, midbrain to pons diameter, and midbrain to pons area ratio in progressive supranuclear palsy (PSP). Marked midbrain atrophy is present in this patient with a hummingbird appearance of the midbrain and pons in the sagittal MRI plane (A). The midbrain to pons diameter ratio is 0.51 (9.23 mm midbrain diameter/18 mm pons diameter) in this patient with cutoff for PSP of 0.52 (A). For the midbrain to pons area ratio, a ratio of the midbrain and pons areas is determined (53 mm$^2$/455 mm$^2$) to be 0.117 with cutoff of 0.12 (B)

FIGURE 4  Morning glory sign. Axial T1 (A) and T2 (B) MRI show lateral concavity and atrophy of the midbrain (white arrows) in a patient with progressive supranuclear palsy

deposition of hyperphosphorylated tau neurofibrillary tangles within the superficial cortical layers. This is in contradistinction to the typical distribution of AD, which is typically seen in deeper cortical layers. Furthermore, the hyperphosphorylated tau deposits in CTE tend to occur in a perivascular distribution with NFTs occurring around small cortical blood vessels. A 2016 National Institute of Neurological Disorders and Stroke/National Institute of Biomedical Imaging and Bioengineering panel defined the pathognomonic lesion for CTE as an irregular accumulation of hyperphosphorylated tau protein within neurons and astroglia around small blood vessels at the depths of cortical sulci.

Imaging characteristics and emerging imaging techniques

There are no imaging features that are specific for the diagnosis of CTE. Structural brain MRI may show some of the gross pathologic features previously mentioned, including generalized cortical atrophy, cavum septum pellucidum, thinning of the corpus callosum, and ventriculomegaly (Figure 7). Advanced MRI techniques such as MR spectroscopy and diffusion tensor imaging are currently under investigation with some success. [$^{18}$F]AV-1451 PET imaging has demonstrated increased radiotracer uptake in former North
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FIGURE 5  MR Parkinsonism index (MRPI). Sagittal and coronal T1 images through the midbrain and pons (A), superior cerebellar peduncle (B), and the middle cerebellar peduncle (C) in a 66-year-old female suspected of having progressive supranuclear palsy (PSP). The MRPI is calculated by taking the ratio of the pons (P) to midbrain (M) areas multiplied by the ratio of the middle cerebellar peduncle (MCP) width to the superior cerebellar peduncle (SCP) width \[\frac{P}{M} \times \frac{MCP}{SCP}\]. The MRPI in this patient was 39.24. An MRPI value of more than 13.55 is abnormal and suggestive of PSP.

FIGURE 6  AV1451 uptake in a patient with progressive supranuclear palsy (PSP). Patients with PSP have been observed to have increased uptake of \[^{18}\text{F}\]AV-1451 (also known as flortaucipir) in the basal ganglia, thalamus, midbrain, subthalamic nuclei, and cerebellar dentate nuclei (B) when compared to healthy control patients (A) as shown above in the figure adapted with permission from Schonhaut et al.\textsuperscript{62}

American football players demonstrating neuropsychiatric symptoms characteristic of CTE,\textsuperscript{88,89} The areas of uptake corresponded with characteristically affected areas of the brain on gross pathology. Furthermore, in one group of former North American football players showing increased uptake of \[^{18}\text{F}\]AV-1451, there was no evidence of abnormally increased amyloid-beta plaque detected by beta-amyloid PET imaging.\textsuperscript{89}

CORTICOBASAL DEGENERATION

Background, significance, and clinical presentation

CBD is a tauopathy first described by Rebeiz et al. in 1967 as a progressive, asymmetric apraxia and akinetic-rigid syndrome.\textsuperscript{90} This classic presentation is now referred to as corticobasal syndrome (CBS) and may include additional cortical findings including myoclonus, alien limb phenomenon, cortical sensory loss, and basal ganglia findings such as bradykinesia and tremor.\textsuperscript{91} The clinical presentation of CBD can vary widely and may appear quite different from the classic CBS presentation. The term CBD is now reserved for the pathologic diagnosis characterized by tau-positive neuronal and glial lesions within a characteristic distribution.\textsuperscript{92} CBD typically occurs in the fifth to seventh decades and has no sex predilection.\textsuperscript{93,94} The prevalence of CBD has been estimated at 4.9-7.3 cases per 100,000.\textsuperscript{95} Disease duration after diagnosis ranges from 2 to 12 years with an average of 6.6 years.\textsuperscript{94,96} As with several other neurodegenerative diseases, pneumonia has been cited as the most frequent cause of death.

The clinical diagnosis of CBD is challenging owing to the marked symptom heterogeneity. There have been four primary phenotypes of CBD identified: classic CBS, nonfluent variant of primary
**Figure 7** Former football player presented in his mid-40s with mild early atrophy and clinical concern for chronic traumatic encephalopathy (CTE). The objective of this figure is to depict the nonspecific findings of CTE via brain MRI early on. In this patient, there is mild enlargement of the lateral (white arrows) and third ventricles with notable thinning of the septum pellucidum and corpus callosum (red arrows). There was also mild nonspecific atrophy of the mesial temporal structures. Molecular image has great potential to better diagnosis CTE in this early stage.

progressive aphasia, frontal behavioral-spatial syndrome, and a primary PSP syndrome.97 The American Academy of Neurology has devised a set of consensus criteria for the diagnosis of probable and possible CBD.97 CBD is noted to be refractory to treatment with levodopa. As with PSP, there are currently no laboratory tests available that specifically diagnose CBD.

**Underlying pathologic mechanism**

The neuropathologic diagnosis of CBD is based primarily upon the histopathologic findings. Gross pathologic findings are helpful but not critical to making the diagnosis. Subtle findings include volume loss and thinning of the cortical gyri predominantly within the parasagittal peri-Rolandic distribution, most often involving the superior frontal gyrus.92 The temporal and occipital lobes are less often involved. 6On histopathology, CBD is characterized by tau-reactive lesions within neurons and glial cells within the cortex and striatum. Additionally, neuronal loss is often seen in focal cortical regions and the substantia nigra.92 One other histopathological feature often considered a hallmark of CBD is the “astrocytic plaque.”98 Like PSP, CBD is also classified as a 4R tauopathy.41

**Imaging characteristics and emerging imaging techniques**

CBD may show asymmetric cerebral atrophy predominantly involving the frontal and parietal lobes on anatomic imaging (Figure 8). The atrophy is often seen contralateral to the clinically affected side.99,100 CBD will also typically demonstrate hyperintense subcortical signal within the affected areas on T2/FLAIR sequences, as well as atrophy of the ipsilateral cerebral peduncle.99,100 Marked tegmental atrophy of the midbrain tegmentum has also been observed, although it is difficult to separate from PSP.

In clinical practice for single patient diagnosis, DAT-SPECT shows inconsistency in differentiating between PD and atypical parkinsonian syndromes (APS) that include multiple system atrophy (MSA), PSP, and CBD.101 However, with the advantage of more advanced imaging in a population-based study analysis of 392 patients with degenerative parkinsonism over a 10-year period, DAT-SPECT imaging analysis using voxel-wise univariate statistical parametric mapping and multivariate pattern recognition using linear discriminant classifiers did show significance in distinguishing PD versus APS (area under the curve [AUC] 0.69) and between APS subtypes (MSA vs. CBD AUC 0.80; MSA vs. PSP AUC 0.69; and CBD vs. PSP AUC 0.69).102 The
FIGURE 8  MRI and 18F-Fluorodeoxyglucose (18F-FDG) PET of an elderly female with suspected corticobasal syndrome. Axial T2 image shows asymmetric right greater than left frontal and parietal atrophy with particular atrophy of the right perirolandic region (white arrows) (A). FDG-PET demonstrated hypometabolism (red arrows) involving the right frontal and right parietal lobe on the coronal view (B & C) and right sagittal view (D). There was notable right thalamic hypometabolism compared to the left (E). Note preservation of activity (yellow arrows) within the temporal lobes (F). The normal left frontoparietal lobe FDG metabolism (yellow arrows) is shown for comparison (G).

analysis illustrated that PD, MSA, PSP, and CBD have distinct patterns of dopaminergic depletion on DAT-SPECT. For instance, CBD had higher uptake in both putamen relative to PD, MSA, and PSP.

CBD can demonstrate FDG hypometabolism within the frontal and parietal cortices, as well as the thalami and caudate nuclei.103–106 The degree of hypometabolism is typically contralateral to the more clinically affected side, mirroring reported anatomic imaging findings (Figure 8). Regional differences in hypometabolism between CBD and other tauopathies may be helpful in distinguishing between diagnoses.106 As with PSP, beta-amyloid PET imaging is unlikely to be of value in the diagnosis of CBD as the disease is not associated with abnormal amyloid deposition. Beta-amyloid PET can help identify underlying AD in those presenting with CBS, and may have an important clinical impact as treatments become more widely available.107 Visuospatial and functional symptoms tend to be more severe in beta-amyloid PET-positive CBS patients with underlying AD, who typically demonstrate asymmetric volume loss along Wernicke’s area at the posterior aspect of the left superior temporal gyrus.107 Technetium-99m ethyl cysteinate dimer SPECT imaging in patients with clinical diagnosis of CBS typically shows hypoperfusion within the frontal and parietal lobes as well as the basal ganglia and thalami, typically contralateral to the clinically more affected side.79

As with PSP, there is a great deal of research being performed on the utility of novel tau-PET agents for the diagnosis of CBD. Several of the same agents examined for PSP have also been studied in patients with CBD, including [18F]AV-1451 and 18F-THK-5351. Multiple studies have shown uptake patterns of both of these tracers that also correlate with the distribution of tau deposition seen on neuropathology.108–112 As previously mentioned with PSP, [18F]AV-1451 has been shown to have off-target binding in cognitively normal patients, potentially confounding imaging findings in the evaluation of patients with clinical evidence of CBD.64,65 18F-THK-5351, on the other hand, has been shown to have fairly specific binding within typically affected areas of the brain, including the frontal and parietal lobes as well as the basal ganglia.110,112 18F-THK-5351 also has a higher affinity for abnormal tau neurofibrillary tangles and shows less off-target binding as previously discussed.

FRONTOTEMPORAL LOBAR DEGENERATION

Background, significance, and clinical presentation

FTLD is a generic umbrella term referring to progressive degeneration of the frontal and temporal lobes. The condition was first described in 1892 by Arnold Pick and was referred to as Pick’s disease, although today that term is now only utilized for a very specific syndrome/pathology. FTLD is recognized to produce three distinct clinical syndromes (Table 2): behavioral-variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA).113 SD and PNFA are occasionally described under an additional broad umbrella of language-related dementia syndromes termed primary progressive aphasia (PPA).

FTLD syndromes typically present within the fifth and seventh decades of life, although presentation can range from the fourth through eighth decades.114–116 There is no significant difference in age of presentation between the three syndromes. The FTLD syndromes are the second leading cause of dementia after AD and account for up to 20% of dementia cases in patients below age 65.115,116 It is not clear if there is any overall gender predisposition among all FTLD syndromes; however, there do appear to be sex differences between the different syndromes.114,115 The overall prevalence of FTLD has been estimated to range from 4 to 22 cases per 100,000.117–119 Median survival after symptom onset has been estimated at 6–11 years.114,115,120–122
syndromes may result in nearly $120,000 annual expense, up to double the cost reported for AD.\textsuperscript{123} Approximately 40% of patients with FTLD have a positive family history, usually with autosomal dominant transmission.\textsuperscript{114,115,124}

The clinical diagnosis of FTLD syndromes can be challenging due to the possibility of symptom overlap with other primary tauopathies such as PSP and CBD. bvFTD is the most common of the FTLD syndromes and typically presents with changes in behavior, personality, and impaired executive functioning.\textsuperscript{113,124,125} Patients with bvFTD also frequently appear apathetic and unmotivated; however, memory function is usually preserved. Patients with SD typically present with a characteristic syndrome of progressive loss of knowledge of word meanings. Patients will forget the meaning of common words, facts, or even people and may experience impaired objected recognition (visual associative agnosia).\textsuperscript{113,124,126,127} SD patients will typically speak fluently; however, the spoken words may not make any sense.\textsuperscript{113,124}

PNFA will present with effortful, nonfluent speech as well as agrammatism. These patients often have troubles comprehending complex sentences, although single word comprehension is usually preserved, helping to distinguish PNFA from SD.\textsuperscript{113,124,127} Patients with advanced PNFA may also develop the behavioral changes and impaired executive functioning seen with bvFTD. Of note, PSP, CBS, and motor neuron diseases such as amyotrophic lateral sclerosis also have underlying FTLD pathology. Lack of reliable laboratory and imaging biomarkers has made the diagnosis of FTLD primarily clinical and there have been several consensus criteria developed to aid evaluation.\textsuperscript{113,128}

### Underlying pathologic mechanism

FTLD shows atrophy of the frontal and/or temporal lobes on gross pathology, although each variant classically has a somewhat distinct pattern of volume loss. The parietal lobes can occasionally be affected but the occipital lobes are almost never involved. bvFTD will classically show symmetric atrophy of the frontal lobes and occasionally the right temporal lobe.\textsuperscript{113,124} SD, on the other hand, classically shows asymmetric atrophy and cortical thinning of the anterior inferior temporal lobes, usually greater on the left side.\textsuperscript{113,124,126,127,129} In cases of SD where right temporal lobe atrophy is greater, patients tend to present with prosopagnosia.\textsuperscript{124,129,130} PNFA classically shows asymmetric left frontal and perisylvian atrophy.\textsuperscript{114,124,127,131} On microscopic evaluation, there is classically cortical microvacuolation and neuronal loss, predominantly within layer II along with gliosis and myelin loss within the underlying white matter.\textsuperscript{114,115,132}

FTLD can also be divided into two broad categories based on the presence or absence of tau inclusions. A form of tau-negative FTLD with ubiquitin positive inclusions, previously referred to as FTLD-U, is the most common form of FTLD comprising around 60% of cases.\textsuperscript{124,133,134} The predominant protein implicated in this condition has been found to be TAR DNA-binding protein 43 (TDP-43).\textsuperscript{135,136}

There are several tauopathies that may underlie FTLD-associated syndromes, of which Pick’s disease (a form of bvFTD) is often considered the prototype syndrome. The typical pathology underlying Pick’s disease is a 3R tauopathy with characteristic spherical deposition of abnormal tau protein within the hippocampi, basal ganglia, and the superficial neocortical layers of the frontal and temporal lobes.\textsuperscript{114,115,137,138} The tauopathies underlying both PSP and CBD may also produce clinical syndromes associated with FTLD, making diagnostic differentiation between these syndromes quite difficult. An additional tauopathy that may be seen with FTLD syndromes is associated with mutations of the microtubule-associated protein tau (MAPT) gene on chromosome 17 and is often referred to as FTDP-17.\textsuperscript{114,115,124} FTDP-17 has been shown to have an autosomal dominant inheritance pattern.\textsuperscript{139} The tau inclusions of FTDP-17 may include both 3R and 4R isoforms.\textsuperscript{114,140} These inherited forms of FTLD associated with MAPT mutations may produce any of the clinical phenotypes of FTLD.\textsuperscript{134,142}

### Imaging characteristics and emerging imaging techniques

The anatomic imaging findings of classic FTLD syndromes follow the patterns of volume loss seen on gross pathology. The volume loss of both bvFTD and svFTD PPA variant are visible and can be highly suggestive on MRI with the right clinical picture (Figure 9). MRI voxel-based morphometry techniques have also shown a difference in patterns of cortical gray matter atrophy with various MAPT mutations, potentially allowing differentiation of different mutations based on imaging.\textsuperscript{142} Additionally, multiple studies have shown the potential for diffusion tensor imaging (DTI) to show distinctive patterns of white matter damage in the various FTLD syndromes.\textsuperscript{130,144–146} Functional MRI has also shown some promise in this area with a few studies demonstrating altered functional connectivity in FTLD syndromes in a pattern that may potentially allow for differentiation from AD.\textsuperscript{130,147,148}

\textsuperscript{18}F-FDG-PET imaging will typically show hypometabolism within the frontal and anterior temporal lobes in a pattern

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**Table 2: Frontotemporal lobar degeneration atrophy patterns by subtype**

| Atrophy pattern                        | Behavioral-variant frontotemporal dementia | Semantic dementia | Progressive nonfluent aphasia |
|----------------------------------------|--------------------------------------------|-------------------|-----------------------------|
| Symmetric frontal and right temporal lobe | Anterior temporal lobe atrophy with left dominance | Left frontal and perisylvian atrophy |
FIGURE 9  MRI and PET showing asymmetric left sided temporal atrophy. T1 coronal (A) and T2 axial (B) sequences depict the asymmetric left temporal lobe volume loss (arrows) indicative of semantic dementia. Note the dramatic temporal lobe volume loss on the left with a knife-like morphology to the left anterior temporal lobe. \(^{18}\)F-Fluorodeoxyglucose PET in the axial (C) and coronal (D) planes shows corresponding hypometabolism in the left temporal lobe with more profound atrophy of the left temporal lobe compared to the right (arrows) corresponding with the gross pathology of the underlying FTLD syndrome (Figure 10).\(^{149,150}\) The parietal lobes may be involved later in the disease process, with the occipital lobes rarely involved. The patterns of hypometabolism on \(^{18}\)F-FDG-PET have also been shown to fairly reliably distinguish FTLD from AD, one of the main clinical diagnostic differential considerations.\(^{151}\) FTLD typically shows no beta-amyloid deposition on beta-amyloid PET imaging with some reported positive cases thought to be potentially secondary to underlying AD mimicking FTLD symptoms.\(^{152,153}\)

In terms of tau-specific PET agents, \[^{18}\text{F}\]AV-1451 has shown binding correlating with tau pathology in some patients with specific MAPT mutations.\(^{154,155}\) Additionally, \[^{18}\text{F}\] has shown potential to differentiated between variants of PPA.\(^{156}\) \[^{18}\text{F}\]AV-1451 has also shown expected uptake in patients with bvFTD and CBS; however, elevated binding has been seen in patients thought to most likely have underlying tau-negative FTLD pathology (ie, FTLD-U), raising concerns regarding the specificity of the tracer in FTLD.\(^{157}\) The previously described issues of off-target binding and increased retention with age seen with \[^{18}\text{F}\]AV-1451 again apply and could potentially limit the utility of this tracer in FTLD evaluation.

\[^{18}\text{F}\]-THK-5351 has been shown to bind in areas correlating with expected tau pathology in language variants of FTLD/PPA, potentially serving as a biomarker for neurodegeneration.\(^{158,159}\) Tau PET imaging with \[^{18}\text{F}\]-THK-5351, however, may also be susceptible to several pitfalls, including off-target binding and binding to MAO-B, potentially confounding evaluation for deposition of abnormal tau protein. Given these findings, \[^{18}\text{F}\]-THK-5351 binding may turn out to be less sensitive for selective detection of abnormal tau deposition; however, there may be utility for its use in monitoring the effects of tau-related inflammatory changes and astrogliosis.\(^{70,72}\)
Further research will be needed to determine the precise role for these novel PET tracers in the diagnosis and monitoring of FTLD-related syndromes.

**CURRENT TAUOPATHY TREATMENT OPTIONS AND EMERGING THERAPIES**

At present, there are no disease-modifying therapies available for the treatment of primary tauopathies, and therapies are limited to those targeting symptoms and supportive management. To further complicate matters, many medications that target specific symptoms of these diseases often worsen other symptoms or have intolerable side effects. Nonpharmacologic treatment options such as speech and physical therapy are critical for limiting further morbidity from these diseases. Multiple potential disease-modifying medications have been studied; however, to date none have convincingly shown benefit in the treatment of tauopathies. Studies assessing the benefits of Coenzyme Q10 in PSP have shown conflicting results. Riluzole has also been studied and has not been shown to have significant benefits on survival or disease progression in PSP.

As previously mentioned, tau is a microtubule-associated protein that is critical for microtubule stability. Under pathologic conditions, however, tau can become abnormally hyperphosphorylated, leading to decreased stability of microtubules as well as formation of toxic aggregates of hyperphosphorylated tau. Therefore, more novel approaches to disease-modifying therapy target tau phosphorylation, kinase inhibition, and microtubule stabilization, among others. Davunetide is a peptide that inhibits tau phosphorylation and promotes microtubule stability and it was hypothesized that it may be beneficial in tauopathy patients. A trial of davunetide in patients with PSP, however, found no benefits. An additional Phase 2 trial of tideglusib, an inhibitor of a kinase contributing to tau hyperphosphorylation, also showed no benefit in patients with PSP. Early-stage trials for other medications including an additional microtubule stabilizer (TPI-287) and an inhibitor of tau acetylation (salsalate) are also ongoing.

The more recently described “prion hypothesis” of tauopathies may also provide a potential target for therapies. This theory also holds that in order for the pathologic intracellular tau aggregates to propagate to neighboring cells, they must first enter the extracellular space and then be internalized by the adjacent cell. Evidence suggests that the pathway of propagation of pathologic tau aggregates may proceed via functional synaptic neuronal connections rather than direct spatial proximity. Anti-tau monoclonal antibodies have been demonstrated to trap these pathologic tau aggregates within the extracellular space and halt internalization by neighboring neurons, suggesting an important role for targeting extracellular tau. Therapies directed against this extracellular tau are some of the latest being researched, including two monoclonal antibodies in Phase 2 trials, ABBV-8E12 (AbbVie) and BIIB092 (Biogen). Both of these trials seek to enroll PSP patients who are relatively early in the disease course.

Multiple therapies targeting tau pathology in patients with AD are also under investigation, and while the studies underway are targeted to AD, the results will be of great interest to patients with primary tauopathies. Several humanized monoclonal antibodies targeting extracellular tau are in Phase 2 clinical trials for AD including RO7105705 and LY3303560. Several other monoclonal antibodies are currently in Phase 1 trials for patients with AD. Additionally, there is an active vaccine (AADvac1) currently in a Phase 2 trial designed to elicit a sustained immune response against pathologic tau species. There is an additional vaccine directed against tau aggregates that is in very early stage human trials (ACI-35). Several additional immunotherapies are currently undergoing preclinical trials.

In addition to immunotherapies, there are several therapeutic approaches targeting tau in patients with AD that are also of interest to the treatment of primary tauopathies. Multiple animal models have suggested potential therapeutic benefit in reducing the amount of total tau, including therapies targeting expression of the tau gene (MAPT). At present, there is an antisense oligonucleotide that targets MAPT mRNA (IONIS MAPTRx) undergoing a Phase 1 trial. Gene-targeting therapies such as this are currently being employed in the therapy of spinal muscular atrophy and Duchenne muscular dystrophy and have even been evaluated for potential treatment in Huntington’s disease. The more recently described “prion hypothesis” of tauopathies may also provide a potential target for therapies. This theory also holds that in order for the pathologic intracellular tau aggregates to propagate to neighboring cells, they must first enter the extracellular space and then be internalized by the adjacent cell. Evidence suggests that the pathway of propagation of pathologic tau aggregates may proceed via functional synaptic neuronal connections rather than direct spatial proximity. Anti-tau monoclonal antibodies have been demonstrated to trap these pathologic tau aggregates within the extracellular space and halt internalization by neighboring neurons, suggesting an important role for targeting extracellular tau. Therapies directed against this extracellular tau are some of the latest being researched, including two monoclonal antibodies in Phase 2 trials, ABBV-8E12 (AbbVie) and BIIB092 (Biogen). Both of these trials seek to enroll PSP patients who are relatively early in the disease course.

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CONCLUSION

Modern medicine is benefitting greatly from the shift away from histologic/pathologic diagnosis toward noninvasive yet highly specific forms of diagnosis, including imaging. Molecular imaging provides a key stepping-stone for not only permitting more specific disease diagnoses, but it also holds great potential for personalized monitoring of the disease progression or therapeutic effect of therapies through the duration of the disease. While the neurodegenerative diseases in general and tauopathies, in particular, have struggled to find significant disease-modifying treatments, coevolution of molecular imaging with therapies will be key to the future of combating these often devastating and debilitating diseases.

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