Imaging pathological tau in atypical parkinsonian disorders

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Abstract

Purpose of review—This review examines the current literature on tau imaging in atypical parkinsonian disorders and other tauopathies.

Recent findings—There are a number of tau PET radiotracers that have demonstrated promising preliminary results in atypical parkinsonian disorders, such as progressive supranuclear palsy and corticobasal degeneration. These radiotracers were capable of selectively labeling tau *in vitro* and *in vivo*, with high affinity. Other radiotracers tested more extensively in patients with Alzheimer's disease have also been able to successfully image tau deposition.

Summary—The development of tau radioligands for PET has led to the current testing of these tracers in clinical studies, many of which concentrate on patients with Alzheimer's disease. Atypical parkinsonian disorders such as progressive supranuclear palsy and corticobasal degeneration are now being investigated as well. These disorders can be very difficult to diagnose, because of their clinical overlap with other parkinsonian disorders. Imaging tau using PET could serve as a diagnostic biomarker for these tauopathies and provide a means of assessing treatment that targets tau burden.

Keywords

atypical parkinsonian disorders; corticobasal degeneration; PET; progressive supranuclear palsy; tauopathy

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Parkinsonism encompasses a multitude of neurodegenerative disorders, the most common being Parkinson's disease. All other parkinsonian disorders fall under the umbrella of atypical parkinsonism [1]. The main atypical parkinsonian disorders are progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies [2]. There can be significant symptom overlap between these movement disorders, making clinical diagnosis very challenging; therefore, the most reliable method of differentiation is pathology [2]. Parkinson's disease, MSA, and dementia with Lewy bodies present with aggregation of α -synuclein, a central nervous system protein, whereas PSP and CBD are characterized by pathological tau [2].

Tau is a microtubule-associated protein that functions to stabilize microtubules and aids with intracellular transport [3]. During pathological conditions, tau is capable of self-aggregation and appears to be toxic to synaptic function [4].

PET can be used to label pathological tau *in vivo*, and tau radioligands have recently been developed and tested in humans. A substantial portion of tau imaging research has focused on one of the most common neurodegenerative diseases, Alzheimer's disease. An increasing number of studies are emerging that involve atypical parkinsonian patients; however, further testing is required to validate tau radioligands in PSP and CBD. A tau radiotracer can serve as a biomarker for the following: diagnosis – especially important for atypical parkinsonian disorders, disease progression, and treatment efficacy.

KEY POINTS

- PSP and CBD are underdiagnosed because of their clinical symptom overlap with other parkinsonian disorders and tauopathies.
- Several PET radioligands have been developed for imaging tauopathies.
- To date, there have been very few radiotracers tested in PSP and CBD.
- Further testing should be performed in atypical parkinsonian disorders to determine the radiotracers' utility in these patient populations.

TAUOPATHIES

Tauopathies are pathologically distinguished by the different isoforms, conformations, and spatial distribution of tau aggregates. The tau protein exists in six isoforms [5–7]. Alternative splicing of exon 10 results in the production of three repeat (3R) tau isoforms and four repeat (4R) tau isoforms [8[■],9]. In healthy adults, the ratio of 3R to 4R isoforms is approximately equal; however, these proportions vary across tauopathies. For example, equal concentrations of 3R and 4R isoforms are seen in Alzheimer's disease, whereas in PSP and CBD, the 4R isoform predominates [5,6,8[■],10]. Parkinsonian tauopathies also differ from Alzheimer's disease in the conformation of their tau aggregates. In Alzheimer's disease, neurofibrillary tangles (NFTs) appear as paired helical filaments (PHFs), whereas in PSP and CBD, tau filaments are straight [7]. A significant post-translational modification made

to tau is phosphorylation. Unphosphorylated tau is largely located in the axons of neurons and aids with intraneuronal transport and microtubule stability, whereas phosphorylated tau cannot bind microtubules and is primarily found in the soma of neurons [5,8[■]]. Increased phosphorylation can produce tau aggregates in both neurons and glial cells [3,5,6,8[■],10,11]. In all tauopathies, tau is hyperphosphorylated, but the distribution of tau load varies for each disease and is correlated with clinical symptoms [3,5,12,13[■]].

In PSP, straight tau filaments appear as NFTs, ‘tufted’ astrocytes, and coiled bodies within oligodendrocytes [7,13[■]]. The brainstem and subcortical structures are predominantly affected; however, cortical areas, particularly, the motor cortex, are also affected [14]. The basal ganglia and brainstem mainly present with NFTs, whereas ‘tufted’ astrocytes are seen to the greatest degree in cortical structures, the caudate nucleus, and the putamen. In most cases of PSP, the subthalamic nucleus, substantia nigra, and globus pallidus internus display coiled bodies [15]. The cardinal symptoms of this neurodegenerative disorder are vertical gaze palsy, gait impairment, postural instability, and bradykinesia – similar to that in Parkinson’s disease [2,16,17]. Cognitive decline is also a prominent nonmotor symptom [16,17].

The hallmark of tau pathology in CBD is astrocytic plaques composed of hyperphosphorylated 4R tau isoforms [6,11,17,18[■],19]. Neuronal and glial aggregates are present in both cortical regions and subcortical structures, such as the striatum [7,18[■],20]. The most predominant motor symptoms include limb rigidity and bradykinesia, which often present in a progressive and asymmetrical manner [18[■],19]. Other symptoms include akinesia, dystonia, ideomotor apraxia, and alien limb phenomena [18[■]]. Similarly to PSP, patients with CBD often develop cognitive impairments [19].

IMAGING TAU

Although there are numerous advantages to imaging tau, developing an appropriate radiotracer for this protein poses many challenges. For instance, tau is an intracellular protein; therefore, the radio-tracer must be able to cross not only the blood-brain barrier, but also the plasma membrane [8[■],20]. An appropriate radiotracer must be capable of binding phosphorylated tau in neurons and glial cells. Due to the heterogeneity of tau isoforms present in different tauopathies, it is important that the radiotracer can bind both 3R and 4R isoforms [8[■],21]. As with all radiotracers, the ligand must have favorable pharmacokinetics, including fast uptake into the brain and rapid washout; be highly selective and have high affinity for tau; and have no radioactive metabolites that cross the blood-brain barrier [8[■]]. Another challenge is the secondary β -sheet structure that tau shares with A β aggregates and α -synuclein, present in Alzheimer’s disease and parkinsonian disorders, respectively [6,7,20]. Owing to the aforementioned obstacles, it may be difficult to develop a tau radioligand appropriate for use in all tauopathies.

Progressive supranuclear palsy

Patients with PSP have been researched in relatively few tau imaging studies; however, as novel radioligands have begun successfully detecting tau in other disorders, such as Alzheimer’s disease, more studies are emerging that test radiotracers in PSP. The probe 2-

(1-6-[(2-[¹⁸F]fluoroethyl)(methyl)amino]-2-naphthylethylidene)malononitrile ([¹⁸F]-FDDNP) was selected for its ability to bind the β -pleated sheet conformation of tau [15]. As previously mentioned, tau shares this conformation with A β plaques and α -synuclein aggregates. It is important for diagnostic purposes of imaging tau in parkinsonian disorders that a tau radiotracer does not bind α -synuclein. When tested in patients with PSP, patients with Parkinson's disease, and healthy controls, binding of [¹⁸F]-FDDNP was significantly increased in the subthalamic area, midbrain region, and cerebellar white matter of patients with PSP. This retention was consistent with the reported tau distribution in PSP. In addition, there was a positive correlation between cortical [¹⁸F]-FDDNP binding and the severity of PSP [15]. These preliminary findings suggest that [¹⁸F]-FDDNP is a suitable candidate for imaging tau in PSP. This radiotracer was capable of significantly distinguishing PSP patients from Parkinson's disease patients, which is critical in the early stages when clinical symptom overlap often impedes a proper diagnosis. Further investigations should be performed using [¹⁸F]-FDDNP in PSP with larger sample sizes and other parkinsonian disorders, such as MSA, to ensure there is no binding to α -synuclein aggregates.

Another radiotracer that has been tested in patients with PSP is [¹⁸F]-T807. This pyridole derivative was initially selected for its ability to selectively bind tau over β -amyloid plaques, its rapid uptake and washout, and minimal nonspecific binding to other common central nervous system targets [22,23]. Although predominantly tested in Alzheimer's disease and mild cognitively impaired patients, Dickerson *et al.* [24] reported positive results when they tested [¹⁸F]-T807 in patients with PSP. There was increased binding of the radiotracer in the brainstem, basal ganglia, subthalamic nucleus, cerebellum, and frontal cortex in patients with PSP. This pattern of binding is consistent with spatial distribution of tau in PSP. [¹⁸F]-T807 displays promise as a diagnostic biomarker, though further testing with PSP patients and other parkinsonian disorder patients should be performed to investigate whether this tracer can significantly distinguish between the groups. Longitudinal PET studies using [¹⁸F]-T807 may provide means of monitoring tau burden once a treatment has been developed. This tracer should also be tested in patients with CBD, because preliminary data points to its ability to image 4R tau isoforms; therefore, it is also likely to be useful to image CBD.

Phenyl / pyridinyl - butadienyl - benzothiazoles / benzothiazoliums (PBBs) were a hit when screening for compounds that would bind β -sheet conformations [25]. Further analysis using brain samples from patients with Alzheimer's disease determined that this class could bind NFTs, neuropil threads, and plaque neurites [26]. Lead optimization yielded the compound [¹¹C]-PBB3, which demonstrated the ability to detect the immunostained tau plaques in PSP brain samples [25,26]. A mouse model with 4R tauopathy was used to confirm the binding of [¹¹C]-PBB3 to this tau isoform [21]. [¹¹C]-PBB3 recently underwent clinical testing in patients with PSP and the highest retention was associated with brain regions responsible for clinical symptoms [27]. Another study with PSP patients reported significantly higher binding of [¹¹C]-PBB3 in globus pallidus, putamen, thalamus, subthalamus, midbrain, pons, and perirhinal areas compared with healthy controls [28]. To evaluate the diagnostic potential of [¹¹C]-PBB3 for patients with PSP, this tracer must be tested in comparison to other parkinsonian disorders, namely, Parkinson's disease and MSA.

Lansoprazole is an FDA-approved proton-pump inhibitor that was developed for tau imaging. Both [^{11}C]-*N*-methyl lansoprazole and [^{18}F]-*N*-methyl lansoprazole demonstrated high affinity and selectivity for tau fibrils over A β plaques in Alzheimer's disease brain samples [13[■]]. Further autoradiography was performed with the radiotracers on PSP brain samples. Both tracer bindings were consistent with the tau immunostaining. Additional testing indicated that there was uptake of the two lansoprazole radiotracers in the brains of nonhuman primates [13[■]]. The next step in testing is to measure uptake and binding in PSP patients, nontauopathy parkinsonian patients, and healthy controls.

Corticobasal degeneration

CBD is a rare disease that is often underdiagnosed; therefore, very few tau imaging clinical studies have involved patients with CBD. The most promising radiotracer thus far is [^{11}C]-PBB3. Double fluorescence staining using this radioligand demonstrated its ability to detect pathological tau within neurons and astrocytic plaques in CBD brain slices [26]. A clinical PET study revealed that [^{11}C]-PBB3 is capable of detecting tau deposits in patients with CBD [26]. When tested by Suhara and Shimada [27[■]], [^{11}C]-PBB3 binding distribution in CBD patients correlated with their symptoms. These results were consistent with another study, reporting significantly increased binding in the supplementary motor area, subthalamus, midbrain, and perirolandic areas of CBD patients compared with healthy controls [28]. PET studies with larger sample sizes should be performed in order to validate this radiotracer in patients with CBD. The binding of [^{11}C]-PBB3 in patients with CBD should be compared with the binding in patients with Alzheimer's disease to test for significant differences. This tracer may be a potential biomarker for the differentiation between Alzheimer's disease and CBD, as well as a means of monitoring tau burden in patients with CBD.

Alzheimer's disease

Clinical testing of radiotracers that detect intracellular tau has primarily involved patients with Alzheimer's disease. Although the tau aggregates in Alzheimer's disease differ in isoform ratio and conformation from PSP and CBD, radiotracers capable of detecting tau in Alzheimer's disease may be applicable to atypical parkinsonisms.

A quinolone derivative, [^{18}F]-THK523, demonstrated the ability to selectively label PHF tau over β -amyloid plaques, in Alzheimer's disease brain samples [29]. When tested in patients with Alzheimer's disease, binding in the temporal cortex and hippocampus was significantly greater than binding in healthy controls. However, this radiotracer was not able to detect tau filaments in brain samples of CBD or PSP [7,10]. Further development of [^{18}F]-THK523 led to two new compounds: [^{18}F]-THK5105 and [^{18}F]-THK5117. These radiotracers demonstrated higher binding affinity for tau aggregates in Alzheimer's disease brain samples than [^{18}F]-THK523 and were selective for tau over A β plaques [30,31]. When tested in patients with Alzheimer's disease, [^{18}F]-THK5105 demonstrated significantly increased binding in the Alzheimer's disease group, compared with the healthy control group [32[■]]. The radiotracer's binding distribution in patients with Alzheimer's disease corresponded to the reported pattern of tau pathology in Alzheimer's disease and increased binding was correlated with disease severity [32[■]]. Clinical testing of [^{18}F]-THK5117 was also

performed in patients with Alzheimer's disease. Uptake in these patients correlated with tau pathology distribution in Alzheimer's disease and associated with cognitive decline [33[■]].

Although initial testing with [¹⁸F]-THK523 failed to label tau aggregates in non-Alzheimer's disease tauopathies, the arylquinolin derivatives [¹⁸F]-THK5105 and [¹⁸F]-THK5117 have demonstrated superior affinity for tau and may be able to label tau deposits in non-Alzheimer's disease tauopathies. In-vitro autoradiography with these radiotracers should be performed on PSP and CBD brain samples and compared with tau immunostaining. If tau deposits are successfully labeled *in vitro*, clinical studies should be performed on patients with PSP and CBD, as well as nontauopathy parkinsonian disorders. The correlation between [¹⁸F]-THK5105 and [¹⁸F]-THK5117 retention and dementia severity in Alzheimer's disease suggests the potential for these tracers to be used for monitoring tau burden in movement disorders. Longitudinal studies using patients with PSP and CBD must be performed in order to track tau pathology progression, and finally, postmortem autopsies will be the absolute confirmation that [¹⁸F]-THK5105 and [¹⁸F]-THK5117 were able to successfully label tau aggregates.

Another group of tau radiotracers, pyridoindole derivatives, have been developed and recently tested in patients with Alzheimer's disease. Owing to the favorable pharmacokinetics of [¹⁸F]-T807 and its selective binding to tau over A β aggregates, as mentioned previously, initial clinical testing yielded promising results in Alzheimer's disease and mild cognitively impaired patients [23]. Another pyridoindole derivative, [¹⁸F]-T808, also demonstrated favorable kinetics, minimal nonspecific binding, and high affinity for tau [34[■]]. In the first clinical study, binding of [¹⁸F]-T808 was significantly higher in patients with Alzheimer's disease compared with healthy controls. Furthermore, the retention pattern in patients with Alzheimer's disease was correlated with the known distribution of PHF tau and dementia severity was associated with increased binding [34[■]]. Testing in patients with PSP and CBD is required to determine the efficacy of [¹⁸F]-T808 imaging tau in atypical parkinsonian disorders.

Frontotemporal dementia

Frontotemporal dementia (FTD) describes clinical syndromes that involve the progressive degeneration of the frontal and temporal lobes [35]. The most common subtype of FTD is behavioral variant FTD (bvFTD); this syndrome presents with tau pathology in approximately 50% of cases [4,13[■],35–37]. BvFTD is underdiagnosed and its clinical symptoms can overlap with those of PSP and CBD [35,36]. To date, two tau radiotracers have been tested in patients with FTD: [¹¹C]-PBB3 and [¹⁸F]-T807. The binding of [¹¹C]-PBB3 was correlated with FTD symptomatology in a preliminary study and [¹⁸F]-T807 binding was increased in the frontal and temporal cortices in a patient with moderately severe FTD [24[■],27[■]].

APPLICATIONS OF TAU IMAGING

The current gold standard for diagnosing PSP and CBD is a postmortem evaluation of neuropathology [2]. Other pathological tests, which include cerebrospinal fluid measuring phosphorylated tau and structural MRI, are not accurate enough for a definitive diagnosis

[17,38]. Diagnosis based on clinical symptoms is not reliable either, because of the large overlap with other parkinsonian disorders. For example, patients with PSP and MSA can both present with supranuclear vertical gaze palsy [15–17]. CBD symptoms vary from patient to patient and it is sometimes misdiagnosed as Alzheimer's disease [18[■],19]. To date, there have not been any diagnostic tests available for early detection of PSP or CBD [16]. As a result, only 25% of patients with PSP are correctly diagnosed and CBD is also greatly underdiagnosed [13[■],16,18[■]].

Methods for monitoring disease progression and testing treatment efficacy are also lacking for tauopathies. Tau load is correlated with disease severity and cognitive decline [3,12,21]. Therefore, monitoring tau burden is indicative of disease advancement and symptom manifestation. In addition, tau can be used as a molecular marker of treatment efficacy. A therapy that slows or decreases tau load is especially important for PSP and CBD because tau aggregation is their main cause [5–8[■],15].

PET is a noninvasive, in-vivo method of imaging pathological tau [39,23]. Not only does it have the potential to detect tau fibrils but it also provides a visual representation of tau distribution within the brain [8[■]]. PET imaging of tau has the potential to differentiate between tauopathies and nontauopathies, such as PSP and Parkinson's disease, and between two tauopathies, such as CBD and Alzheimer's disease. A substantial advantage to early diagnosis is the detection of tau pathology before detrimental neuronal loss has occurred. With new therapeutics targeting tau burden in the initial clinical stages, an early diagnostic tool will be essential to optimize treatment efficacy.

CONCLUSION

Research focusing on tau PET imaging has considerably increased in the past few years and recent studies have begun to include non-Alzheimer's disease tauopathies. Atypical parkinsonian disorders can be very difficult to diagnose clinically, especially in the early stages, and it is for this reason that future studies using tau radioligands should focus on PSP and CBD in order to establish a validated diagnostic biomarker. Furthermore, as treatments targeting tau burden approach the clinical trial stages, a tau radio-ligand would be invaluable for determining their molecular efficacy *in vivo*.

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