

# Rare Tauopathies

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## Abstract

Tauopathies are rare neurodegenerative disorders related to microtubule-associated protein tau, which functions to stabilize microtubules. Pathological changes caused by overexpression or hyperphosphorylation of tau lead to the disengagement of tau from microtubules and accumulation of toxic intracellular inclusions. Tau pathology is the underlying mechanism for several sporadic and genetic disorders. These are collectively known as tauopathies. Each tauopathy is differentiated from others by its neuropathological features such as the presence of specific isoforms of tau, type of cellular inclusions, and the regions of the brain affected. Neuropathological features, with a few exceptions however, do not correspond to distinct clinical phenotypes. There is considerable phenotypic overlap between the different tauopathies. Interaction between tau and other protein inclusions further alters the clinical phenotype. Recent advances in the development of tau biomarkers, especially the development of tau radioligands used in positron emission tomography neuroimaging, and a better understanding of biology and pathology of tau are important first steps toward the ultimate goal of accurate diagnosis and disease modification in tauopathies.

## Keywords

- ▶ tau
- ▶ tau-PET
- ▶ MAPT
- ▶ FTLD-tau

Primary tauopathies are a diverse group of sporadic or genetic neurodegenerative disorders characterized by the aggregation and dysfunction of tau protein. Tauopathies are classified based on their neuropathological phenotype. Tau-related frontotemporal lobar degeneration (FTLD), designated FTLD-tau, is the umbrella term for progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease or Pick body disease.<sup>1</sup> Other pathological entities such as argyrophilic grain (AG) disease (AGD), primary age-related tauopathy (PART), aging-related tau astroglial pathology (ARTAG), and globular glial tauopathy (GGT) are now also recognized as primary tau-related disorders.<sup>2</sup> Clinical features and neuropathological findings of these conditions will be discussed in detail. We will also briefly review disorders where tau pathology is present but is not considered to play the primary role in pathogenesis.

In tauopathies, with rare exceptions, correlation between neuropathology and clinical phenotype is poor. The high degree of clinical overlap between different tauopathies limits the specificity of the clinical diagnosis. The gold standard for the diagnosis is neuropathology, but the development of tau

radioligands has opened several new avenues for research and antemortem diagnosis of tauopathies. The ultimate goal is to develop biomarkers specific to tauopathies, enabling clinical trials of disease-modifying therapies. In this review, we will discuss tau protein biology and pathophysiology, tau interactions with other proteinopathies, and a diagnostic and management approach to tauopathies.

## Tau biology and Pathogenesis

Tubulin associated unit or "tau" is a microtubule binding protein that is required for microtubule assembly.<sup>3</sup> In neuronal axons, microtubules are essential for axonal transport, cytoskeletal integrity, and polarization.<sup>4</sup> Tau also serves an important role in the function of astrocytes and oligodendrocytes.<sup>5</sup>

Tau protein is encoded for by the microtubule-associated protein tau (*MAPT*) gene on chromosome 17q21–22,<sup>6</sup> which exists as two haplotypes. The H1c haplotype has been associated with a higher risk of tauopathies compared with the H2 haplotype.<sup>7</sup> To understand the role of tau in pathology, it is important to understand its native structure. The

protein is comprised of four domains: the N-terminal region, a central proline-rich region, a microtubule binding domain, and the C-terminal region. The microtubule binding domain contains several repeated motifs for binding microtubules. Alternative splicing of exons 2, 3, and 10 gives rise to six distinct isoforms of tau. In the microtubule binding domain, three or four microtubule binding repeat motifs are seen depending on whether exon 10 is spliced out or retained, respectively.<sup>6,8</sup> The corresponding isoforms are called 3R and 4R tau. The relative predominance of isoforms varies during stages of life and in different brain regions. The 4R isoform predominates in certain tauopathies such as PSP and CBD, whereas 3R tau is associated with Pick's disease. Isoforms may even vary between different clinical phenotypes of the same neuropathological condition.<sup>9</sup>

There are several mechanisms by which the tau protein plays a role in the pathogenesis of neurodegenerative disease. Tau hyperphosphorylation is one of the most well recognized pathogenic changes. In the phosphorylated state, tau disengages from microtubules, causing depolymerization, whereas dephosphorylation causes rapid reversal of this phenomenon, allowing microtubule assembly to occur.<sup>10</sup> Tau phosphorylation is therefore an important pathogenic event and is implicated in microtubule dysfunction and accumulation of hyperphosphorylated tau aggregates.<sup>8</sup> Other posttranslational modifications may also affect tau function, including O-linked N-acetylglucosamine modification, ubiquitination, nitration, oxidation, methylation, and acetylation.<sup>11</sup> Altered tau protein causes neuronal and glial dysfunction by affecting microtubules, leading to impaired axonal transport, altered synaptic connectivity, and mislocalization of tau to the somatodendritic compartment.<sup>8,12,13</sup> Disproportionate increase in the level of 4R tau isoform has also been considered neurotoxic due to its greater propensity for hyperphosphorylation and aggregation.<sup>14</sup> As demonstrated in a mouse model, once hyperphosphorylated, tau aggregates can induce pathological conformational changes in normal tau protein leading to tau inclusions in normal brain tissue.<sup>15</sup> Tau has been hypothesized to spread in a prion-like manner via microglia, or transsynaptically throughout the anatomically and functionally connected regions.<sup>16</sup>

Other cellular proteins may independently influence tau expression and pathogenesis. For example, amyloid  $\beta$  induces binding of fyn (a Src family nonreceptor tyrosine kinase) to the proline-rich region of tau, enabling it to cause N-methyl-D-aspartate receptor-mediated excitotoxicity.<sup>17</sup> Another example relates to transactive response deoxyribonucleic acid binding protein of 43 kDa (TDP-43) which promotes inclusion of exon 10 in tau messenger ribonucleic acid (mRNA), increasing the expression of 4R tau isoform.<sup>18</sup> These pathogenic changes may occur sporadically, or secondary to genetic mutations. Genetic mechanisms underlying tauopathies will be reviewed in the next section.

## Genetic Tauopathies

Several genetic mutations have been implicated in causing tauopathies, most importantly those involving the *MAPT*

gene. Although these are classified separately from sporadic tauopathies,<sup>19,20</sup> the neuropathological findings resulting from certain *MAPT* mutations are indistinguishable from sporadic FTLD-tau subtypes.<sup>21,22</sup> This is a significant finding, as genetic cases can serve as a disease model to study cellular pathogenesis and disease mechanisms, which could then be extrapolated to sporadic disease. *MAPT* H1 haplotype, specially the H1/H1 genotype, confers increased risk of 4R tauopathies such as PSP, CBD, and AGD.<sup>7,23,24</sup> At least 50 single nucleotide polymorphisms and variants of *MAPT* have been associated with an increased risk of FTLD-tau, including A152T, p.S285R, G303V, P301L, S305S, rs8070723, and p.s285R, to name a few.<sup>25–29</sup> Other genes may also lead to clinical and neuropathological features reminiscent of sporadic FTLD-tau, including chromosome 9 open reading frame mutations, myelin-associated oligodendrocyte basic protein, Syntaxin 6, eukaryotic translation initiation factor 2-alpha kinase 3, dynactin, C-X-C motif chemokine receptor 4, and estimated glomerular filtration rate.<sup>30–33</sup>

## Pathologic Diagnoses

### Progressive Supranuclear Palsy

PSP is a neuropathologically defined 4R tauopathy which corresponds clinically to Steele–Richardson–Olszewski syndrome, named after its original describers in 1964.<sup>34</sup> Features include astrocytes containing hyperphosphorylated tau cytoplasmic inclusions, called “tufted astrocytes,” and dense inclusions in neurons called “globose neurofibrillary tangles.” These changes are associated with neuronal loss and gliosis predominantly in the globus pallidus, subthalamic nucleus, and substantia nigra. On gross examination of the brain, mild frontal lobe atrophy, midbrain atrophy, dilation of the aqueduct, and depigmentation of both the locus coeruleus and substantia nigra are seen.<sup>35,36</sup>

The classic clinical presentation of PSP, Richardson–Olszewski syndrome, is characterized by prominent postural instability, vertical supranuclear gaze palsy, and akinetic rigidity.<sup>37</sup> Akin to other neurodegenerative proteinopathies, PSP has been associated with many additional phenotypes that are thus far attributed to anatomical variations in cell loss and tau deposition. Accumulation of tau pathology and cell loss predominantly in the brainstem and basal ganglia result in postural instability and gait freezing (previously known as progressive freezing of gait).<sup>38,39</sup> Some patients with PSP may present with a Parkinson's disease (PD)-like picture with asymmetric parkinsonism that may be somewhat levodopa responsive, often carrying a diagnosis of PD early during the disease course.<sup>40</sup> Spread of tau pathology to cortical areas leads to cortical presentations which may resemble corticobasal syndrome (CBS; see below for more discussion), primary progressive aphasia (PPA), primary progressive apraxia of speech, as well as having other frontal dysexecutive features.<sup>41–46</sup> Extraocular movement abnormalities, especially vertical supranuclear gaze palsy, may occur with any of the above syndromes and is most classically associated with PSP–Richardson syndrome. Other ocular manifestations include square wave jerks, slow vertical

saccades, and apraxia of eyelid opening. The diversity of clinical phenotypes associated with PSP were recognized in the Movement Disorders Society PSP criteria in 2017.<sup>20</sup> According to a recent article, progressive gait freezing and vertical supranuclear gaze palsy remain the most specific and highly predictive of PSP pathology.<sup>47</sup>

### Corticobasal Degeneration

CBD is also a neuropathologically defined 4R tauopathy characterized by neurofibrillary tangles, spherical inclusions (corticobasal bodies), ballooned achromatic neurons, and the most characteristic lesion, the astrocytic plaque.<sup>48</sup> On gross examination, there is usually asymmetric cortical atrophy in the frontoparietal region and depigmentation of substantia nigra with preservation of the locus coeruleus.<sup>48</sup> Based on anatomical distribution, the clinical phenotype associated with CBD pathology may be highly variable, making ante-mortem diagnosis extremely challenging. The most recent diagnostic criteria put forward in 2013 requires a progressive course of over 1 year in an individual over 50 years of age, and recognizes four clinical phenotypes including CBS, frontal behavioral-spatial syndrome, nonfluent/agrammatic PPA, and PSP-like syndrome (PSPS).<sup>19</sup> CBS presents with asymmetric levodopa-resistant parkinsonism, dystonia, myoclonus, asymmetrical limb apraxia, cortical sensory neglect, or even alien limb phenomenon. Even though CBS is most often thought to signify CBD pathology, only 5 of 21 CBS cases in a Queen Square Brain Bank series had CBD pathology.<sup>49</sup> In this cohort, 42% of CBD cases presented with PSP-like clinical syndrome, and 29% of patients who presented with CBS had PSP neuropathology. So far, the understanding is that the clinical presentation of CBD depends on the anatomical distribution of pathology. For example, CBD-CBS had greater tau burden in primary motor, somatosensory cortices, and the putamen, whereas those with a PSPS had greater tau pathology in the limbic regions and hindbrain structures.<sup>50</sup> The most recent diagnostic criteria by Armstrong et al expands the recognized clinical phenotypes of CBD, leading to potentially higher sensitivity but lower specificity.<sup>51</sup>

### Pick's Disease

Pick's disease is a predominantly 3R tauopathy.<sup>52</sup> Gross neuropathological exam shows significant anterior temporal and frontal lobe atrophy. Microscopic examination shows spongiosis, gliosis, cortical pyramidal cell loss, and ballooned neurons called "Pick cells" containing granulofilamentous tau deposits, and "Pick bodies" composed of mainly 3R tau paired helical filaments.<sup>53</sup> Extensive gliosis and myelin loss in the surrounding white matter is commonly seen in severely affected areas. Amygdala, hippocampus, limbic system, and entorhinal cortex are commonly the most severely affected.<sup>54</sup> Patients often present with a behavioral variant frontotemporal dementia syndrome (bvFTD), progressive aphasia, and apraxia of speech.<sup>55-57</sup>

### Globular Glial Tauopathy

GGT is a 4R tauopathy characterized by granular filamentous tau deposits primarily in the cytoplasm of oligodendroglia and

astroglial cells. This may be accompanied by tangle and pre-tangle changes in the neurons. However, the hallmark is white matter glial tau pathology.<sup>58</sup> The clinical syndrome is related to the anatomical location of tau pathology. Josephs et al described 12 cases where glial 4R tau inclusions were noted in the motor and premotor cortices and their associated white matter tracts.<sup>59</sup> Clinical features include parkinsonism, apraxia, upper motor neuron pattern of weakness, and falls. Premortem diagnoses, as expected, ranged from PSP to CBD and Alzheimer's disease (AD). Neuropathologically, these cases were distinct from PSP, hence dubbed atypical PSP.<sup>59</sup> When these pathological changes affect primarily the frontotemporal cortices, patients may present with bvFTD.<sup>60</sup> Variation in neuropathological distribution and clinical phenotypes has been recognized in the consensus criteria for GGT, which classifies it into three types.<sup>58</sup> Type I cases have frontotemporal pathology and present with a frontotemporal dementia, type II cases present with a pyramidal syndrome and have corticospinal tract changes,<sup>59</sup> and type III cases have a combination of frontotemporal and motor pathway pathology, leading to a mixed FTD and motor neuron disease presentation.<sup>58</sup>

### Argyrophilic Grain Disease

AGD was first described by Braak and Braak in a cohort of adult onset dementia patients. A small subset was found to have spindle-shaped argyrophilic deposits in the pyramidal cells of CA1 region of the entorhinal region.<sup>61</sup> AGs are spindle- or comma-shaped deposits composed of 4R tau immunoreactive straight filaments located in neuronal dendrites in the amygdala, entorhinal cortex, and hippocampus.<sup>23</sup> AGD occurs with a greater frequency in patients with PSP and CBD compared with controls, potentially suggesting a common pathogenic pathway for 4R tauopathies.<sup>23</sup> A staging system has been suggested based on 1,405 serial autopsy cases.<sup>62</sup> Stage 0 is the complete absence of AG; stage I: AG cluster in the anterior parahippocampal cortex; stage II: AG spread beyond the anterior parahippocampal gyrus to involve the amygdala, posterior transentorhinal cortex, and anterior medial temporal lobe; and stage III where AG shows clear spread beyond the temporal lobe involving the gyrus rectus, insular cortex, anterior cingulate, septal nuclei, and nucleus accumbens with spongiform changes of the parahippocampal gyrus.<sup>62</sup> However, it is important to note that AGD is also found in cognitively normal subjects.<sup>63,64</sup> Patients who develop amnesic dementia secondary to AGD are significantly more likely to have higher Braak stage and gray matter volume loss in the amygdala/hippocampal complex, frequently occurring in the right brain.<sup>65</sup> It is unclear whether AGD represents an independent disease process or is an age-related pathology.

### Primary Age-Related Tauopathy

PART is an increasingly well recognized condition that is characterized by 3R + 4R paired helical filament tau deposition in the medial temporal lobe structures with minimal to no  $\beta$  amyloid.<sup>66</sup> Neuropathologically, there is evidence of intraneuronal tau immunoreactive neurofibrillary tangles with a Braak stage III or lower. Definite PART is defined by

the absence of amyloid (Thal stage 0), whereas possible PART may have minimal  $\beta$  amyloid (Thal stage 1–2).<sup>67</sup> Patients with symptomatic PART (previously known as tangle predominant dementia) present with cognitive impairment and infrequently dementia, related to the anterior predominant hippocampal atrophy and the resulting cognitive slowing.<sup>68</sup>

There is debate as to whether PART represents a distinct condition or a precursor of AD, and whether patients with PART will develop amyloid pathology over time. However, PART has some important features which sets it apart from AD. Patients tend to be older and live longer than their AD counterparts. Patients with “symptomatic PART” have a much higher density of neurofibrillary tangles compared with early stage AD patients.<sup>69</sup> PART is associated with the presence of  $\epsilon 2$  and  $\epsilon 3$  alleles, but has a much lower rate of  $\epsilon 4$  allele which is strongly associated with AD.<sup>67</sup> A better understanding of PART is needed, and it most likely represents an independent disease process which may occur in conjunction with other neuropathologies. Individuals with PART may be good subjects for studies on the effect of tau in the absence of  $\beta$  amyloid. Prospective studies using molecular positron emission tomography (PET) imaging may help elucidate the effects of PART on clinical symptoms, and its influence on other neuropathologies.

### Aging-Related Tau Astrogliopathies

ARTAG is a term applied to a range of astroglial 4R phosphorylated tau lesions that are distinct from those described above. Astroglial tau pathology tends to be more common after age 60 and may coexist with primary tauopathies or other disorders; however, its effect if any on clinical phenotype is not completely understood.<sup>70</sup> Histopathologically, there are thorn-shaped astrocytes in the white matter and clusters of astrocytes with cytoplasmic perinuclear fibrillary tau deposit in the gray matter. Lesions can also be seen in the subpial, subependymal, and perivascular regions.<sup>70</sup> The amygdala tends to be affected, and the overall distribution of lesions varies in the presence of AD versus primary 4R tauopathies.<sup>71</sup> Factors that play a role in brain–fluid balance may be involved in the pathogenesis of ARTAG, as evidenced by colocalization of connexin-43 and aquaporin-4 with ARTAG-related changes.<sup>72</sup> Whether the presence of ARTAG causes specific clinical syndromes or influences the phenotype of concurrently present neuropathology is not completely known.

### Other Disorders with Tau Accumulation

Several disorders demonstrate neuropathological evidence of tau protein deposition, but tau may not play the sole or primary role in many of these diseases. For example, in AD, tau and amyloid play an equally important role in pathogenesis.<sup>73</sup> In PD and in multisystem atrophy,  $\alpha$  synuclein can indirectly deplete tau affecting microtubule assembly.<sup>74</sup> Tau inclusions in glial cells have been seen in many unrelated diseases including Niemann–Pick disease type C,<sup>75</sup> pantothenate kinase-associated neurodegeneration,<sup>76</sup> cerebrotendi-

nous xanthomatosis,<sup>77</sup> prion disease,<sup>78</sup> subacute sclerosing panencephalitis,<sup>79</sup> and postencephalitic parkinsonism.<sup>80</sup> The significance of these findings are not yet established.

Chronic traumatic encephalopathy (CTE) is an increasingly well recognized progressive tauopathy that results from chronic repetitive head trauma.<sup>81</sup> Commonly encountered in contact sports athletes and military personnel, symptoms include irritability, aggression, suicidality, and forgetfulness; this syndrome is characterized by hyperphosphorylated tau and TDP-43 pathology.<sup>82</sup> CTE is diagnosed neuropathologically at autopsy. Perivascular neuronal and glial intracytoplasmic phosphorylated tau deposits at sulcal depths distinguish this condition from other neurodegenerative tauopathies.<sup>83</sup>

### Clinical Diagnosis

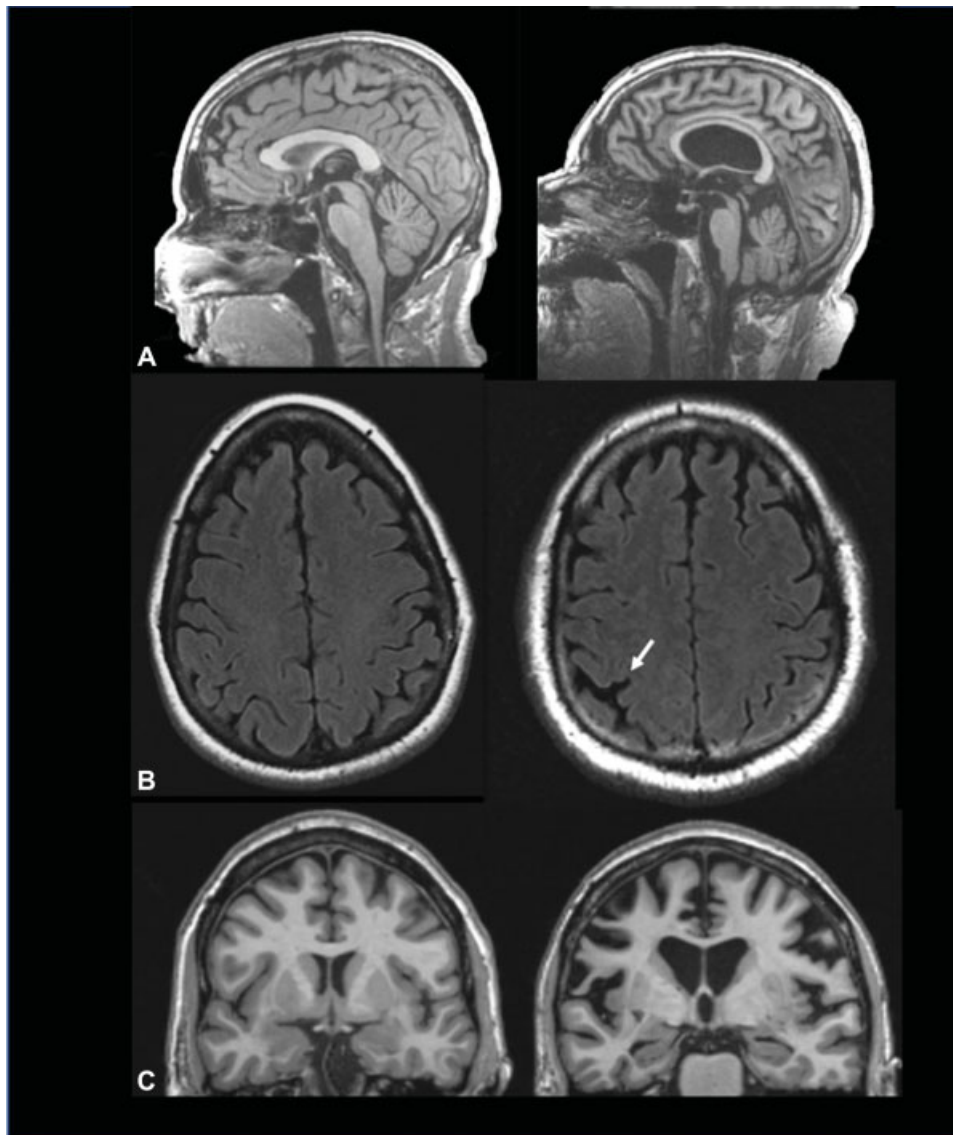
Tauopathies have overlapping clinical features, and therefore prediction of neuropathology by clinical phenotype alone is usually imperfect. The gold standard for diagnosis is neuropathology based on distinguishing features of each pathology. There have been considerable efforts directed toward the development of disease-specific biomarkers to enable antemortem diagnosis and accurate prediction of neuropathology, with the main goal of targeting disease-modifying therapy.

Plasma neurofilament level is a potential biomarker of neurodegeneration and is elevated in PSP.<sup>84</sup> Cerebrospinal fluid (CSF) neurofilament level is elevated in all FTLN syndromes,<sup>85</sup> whereas a panel of nine neurofilament-based biomarkers was able to distinguish PD from Richardson syndrome and CBS, but could not make a distinction between the latter two syndromes.<sup>86</sup> Low levels of  $\beta$  amyloid in the CSF have been reported in PSP, CBD, and AD.<sup>87</sup> Overall, plasma and CSF markers of neurodegeneration are likely to be highly nonspecific with limited meaningful diagnostic value.

Neuroimaging-based markers offer a noninvasive way to potentially predict neuropathology. Structural and functional imaging modalities correlate with clinical phenotype and areas of neurodegeneration, but are not highly specific to neuropathology. Recent advent of tau protein radioligands offers a closer window into neuropathology; however, target of the radioligand should inform interpretation of images.

Magnetic resonance imaging (MRI) and voxel-based morphometry show regional patterns of atrophy in tauopathies (see ► Fig. 1). Patients presenting with CBS, from either PSP or CBD pathology, have a similar pattern of atrophy involving the frontoparietal gray matter and corresponding subcortical white matter.<sup>88</sup> In other words, the pattern of atrophy corresponds more to the clinical syndrome than neuropathological phenotype.<sup>89</sup> PSP has been associated with various radiological markers of brainstem atrophy such as the “humming bird sign” and “morning glory sign.”<sup>90</sup> Atrophy of the midbrain is associated with the PSP–Richardson syndrome phenotype but is not predictive of neuropathology.<sup>91</sup> Studies looking at frontotemporal lobar degeneration syndromes find frontal and temporal lobe atrophy in all cases regardless of neuropathology.<sup>92</sup> Some earlier studies using MRI volumetry found some regional predilections for specific





**Fig. 1** MRI findings in tauopathies. All panels show normal images for comparison on the left. (A) Midbrain atrophy with the “humming bird sign” on sagittal T1-weighted imaging. (B, arrow) CBS with asymmetric superior parietal atrophy on axial FLAIR sequence. (C) Frontotemporal atrophy in Pick’s disease on a coronal MPRAGE sequence. Abbreviations: CBS, corticobasal syndrome; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; MPRAGE, magnetization prepared rapid acquisition gradient echo.

neuropathology/genetic phenotypes. For example, individuals with disease causing CR9ORF72, associated with TDP-43, had a predilection for frontal lobes and parietal lobes.<sup>93</sup>

Like structural MRI, diffusion tensor MRI (DTI) correlates with clinical phenotypes. DTI technique uses mean diffusivity of water molecules as a surrogate marker for white matter tract integrity and function. Clinical phenotype again may suggest a subtype of neuropathology, but a considerable degree of overlap exist, which makes clinical judgment nonspecific. A study comparing patients with PSPS (9 of 18 confirmed PSP pathology) to CBS found several areas of overlapping abnormalities to exist, including in the corpus callosum, superior cerebellar peduncle, medial cingulum, premotor, and prefrontal white matter.<sup>94</sup> A CBS-like presentation was associated with greater DTI abnormalities in the splenium of the corpus callosum, parietal, and premotor cortices compared with PSPS, where

the infratentorial brainstem regions were more significantly affected.

18-Fluorodeoxyglucose PET (FDG-PET) patterns of hypometabolism have been evaluated in autopsy-proven cases of 4R tauopathies.<sup>95</sup> Hypometabolism in the caudate, thalamus, midbrain, and supplementary motor cortex occurred in PSP and other 4R tauopathies. FDG-PET patterns correlate with the clinical phenotype, areas of neurodegeneration, and anatomical tau deposition.<sup>96</sup>

Radioligands with specific binding to tau protein inclusions were developed primarily for AD research, and have enabled imaging of proteinopathies, providing a window into neuropathology during life. The first generation of tau radioligands were developed to bind paired helical filament tau composed of 3R and 4R isoforms, such as 18F-T807, also known as AV-1451.<sup>97</sup> Other tracers include 11C-PBB3, THK-5351, and THK-5117.<sup>98</sup> AV-1451 is the most commonly reported radioligand and has a

higher binding affinity to tau deposits in AD compared with straight filament 4R predominant tau as seen in PSP.<sup>99</sup> In comparison, 11C-PBB3 may have a slightly higher affinity for non-AD type tau found in PSP.<sup>100</sup> Tau-PET studies in probable clinical PSP have shown radioligand uptake in the pallidum, dentate nucleus of the cerebellum, thalamus, caudate, and frontal regions.<sup>101–103</sup> Similarly, in CBS, including some cases with pathologically conformed CBD, tau radioligand uptake is reported in the thalamus, globus pallidus, midbrain precentral cortex, rolandic operculum, supplementary cortex, and associated subcortical white matter.<sup>104–106</sup> See ▶Fig. 2 for tau-PET in tauopathies. These imaging finding should be interpreted carefully because variable binding of tau radioligands to deep gray structures is seen in the control population. Off-target binding to neuromelanin, iron deposits, calcification, choroid plexus, and leptomenigeal neuromelanin also occurs.<sup>107</sup> Auto-

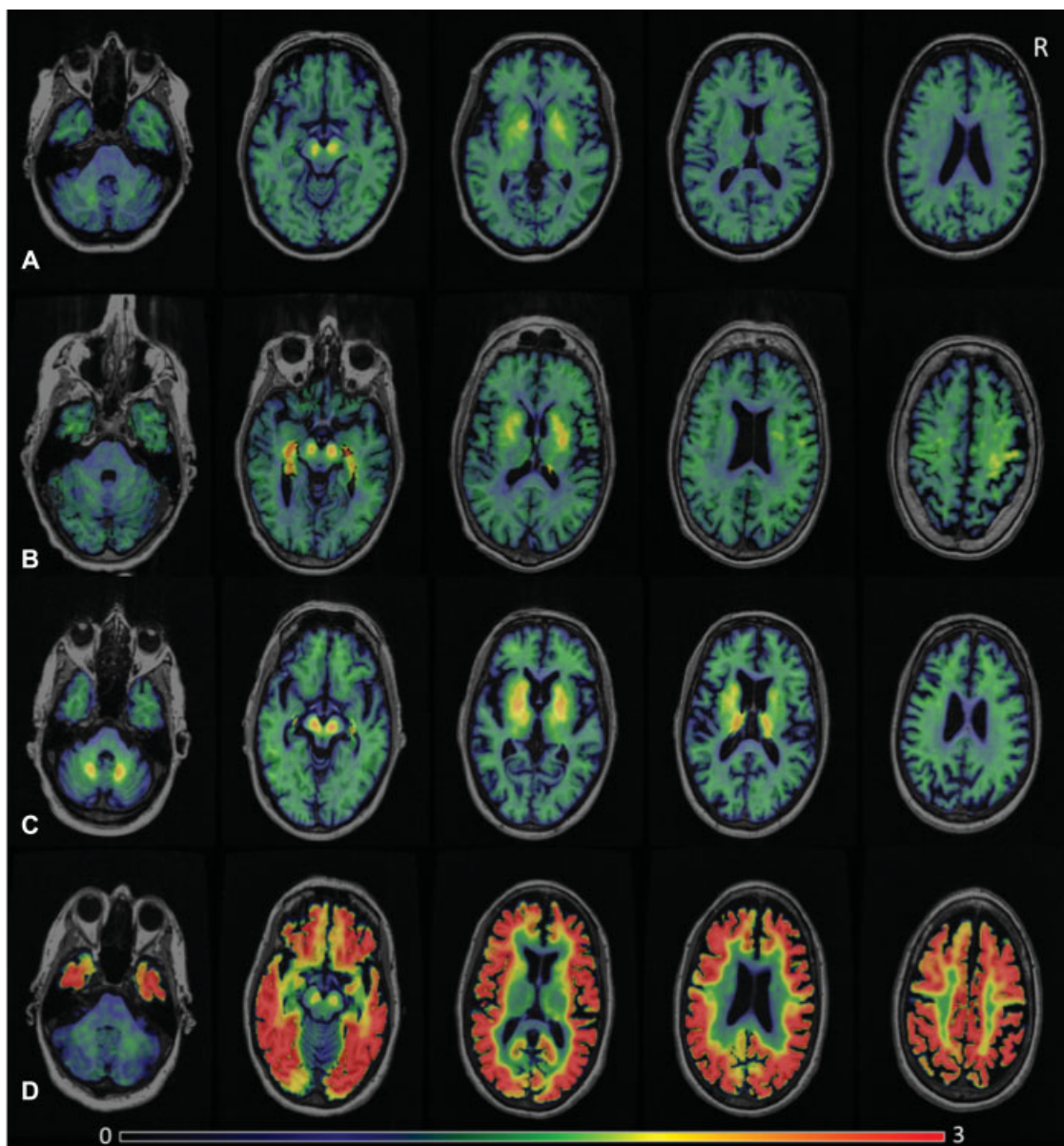
radiography of pathological brain specimens shows faint binding of AV-1451 to 3R and 4R tau,<sup>99,107</sup> and tau neuropathology in PSP shows poor correlation with AV-1451 tau-PET.<sup>96</sup>

Tau-directed PET imaging has the potential of predicting neuropathology in patients, providing a biomarker for the evaluation of disease-modifying drugs. However, further work is required to develop tau radioligands specific to different isoforms for higher specificity.

## Treatment

### Symptomatic

Thus far, no disease-modifying therapies are available for tauopathies. Management strategies are targeted toward alleviation of symptoms. Available treatments have been summarized in ▶Table 1.<sup>108–111</sup>



**Fig. 2** AV-1451 Tau-positron emission tomography (PET) in tauopathies. (A) Normal control. (B) CBS (note off target choroid plexus binding), (C) PSP, and (D) AD. Note the significantly more avid binding of tau radioligands in AD. Abbreviations: AD, Alzheimer's disease; CBS, corticobasal syndrome; PSP, progressive supranuclear palsy.

**Table 1** Symptomatic therapies in tauopathies

Symptom	Management recommendation
Blepharospasm Apraxia of eyelid opening	Botulinum toxin
Focal limb dystonia	Botulinum toxin
Sialorrhea	Botulinum toxin
Diplopia	Prisms
Parkinsonism–bradykinesias and rigidity	Levodopa (oral or via intestinal gel) Physical therapy and rehabilitation
Myoclonus	Levetiracetam, clonazepam
Dysphagia	Prompt evaluation of swallowing function, modification of food/fluid consistency, percutaneous gastrostomy
Hypersomnolence	Caffeine and prescription stimulants
End of life	Goals of care discussion and involvement of palliative care specialists early in the course

### Disease Modifying

Knowledge of tau biology and its role in cellular pathogenesis of primary tauopathies has led to the investigation of a few possible disease-modifying agents; however, clinical trials have been infrequent. The glycogen synthase kinase-3 inhibitor tideglusib, theoretically thought to reduce tau hyperphosphorylation, did not lead to clinical improvement or change in the course of disease progression in clinical trials.<sup>112</sup> Similarly, davunetide, a microtubule stabilizer capable of reducing tau hyperphosphorylation, failed to show clinically significant benefit in human studies.<sup>113</sup> Riluzole was investigated due to its potential for neuroprotection and countering excitotoxicity, but was unsuccessful.<sup>114</sup> An emerging area of excitement is the use of tau-directed immunotherapies including antitau immunoglobulins, as forms of passive immunization, with the goal of employing the immune system to clear extracellular tau deposits.<sup>115</sup> Although some groups have shown reduction of tau burden and improvement in cognition in animal models,<sup>116,117</sup> results are not consistently replicated and concerns exist regarding the risk of neuroinflammation and inability to target intracellular pathology.<sup>118</sup> Immunization strategies have so far been unsuccessful in AD where most agents were directed toward  $\beta$  amyloid.<sup>119,120</sup> These unsuccessful drug trials reiterate the importance of understanding details of cellular processes in neurodegenerative diseases to target the critical pathogenic event early enough in the disease course. There is growing interest in targeting intracellular tau deposits using intrabodies, which can target various isoforms in a highly specific manner<sup>121</sup> and antisense oligonucleotides that can suppress or modify tau mRNA preventing overexpression.<sup>122,123</sup>

Keys to a successful therapeutic intervention are (1) to target the culprit pathogenic step and to do so early enough in the course; (2) gain support from robust preclinical models; and (3) confirm target engagement and effect by disease-specific biomarkers.

### Future Directions

Tauopathies are a group of neurodegenerative disorders that encompass multiple neuropathological conditions and their resulting clinical manifestations. MAPT dysfunction is an important pathogenic event. However, we have an incomplete understanding of inciting physiological factors, prevalence of specific isoform, and mechanisms leading to neurodegeneration. Understanding these cellular processes is essential for developing disease-specific imaging biomarkers and drug targets. Clinical evaluation of these patients is challenging, with many overlapping phenotypes and incompletely understood influence of other proteins. Tauopathies are a group of diverse neuropathologies, and our knowledge of these conditions will continue to grow in the coming years.

#### Conflict of Interest

None declared.

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