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Current Understanding of Neurodegenerative Diseases Associated With the Protein Tau

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Abstract

The primary tauopathies are a group of neurodegenerative diseases in which tau is believed to be the major contributing factor of the neurodegenerative process. In the primary tauopathies, there is a disassociation between tau, a microtubule associated protein, and microtubules, as a result of tau hyperphosphorylation. This disassociation between tau and microtubules results in tau fibrillization and inclusion formation, and microtubule dysfunction. There are different clinical syndromes associated with different primary tauopathies, and some clinical syndromes can be associated with multiple primary tauopathies. Hence, while some clinical syndromes are highly specific and almost diagnostic of a primary tauopathy, many are not, making it difficult to diagnose a primary tauopathy. Recently, radioligands that bind to tau and can be combined with positron emission tomography to detect fibrillary tau antemortem have been developed, although preliminary data suggest that these ligands may not be very sensitive in detecting tau associated with many of the primary tauopathies. Another recent advancement in the field is evidence demonstrating that tau may show similar properties to prions although infective transmission has not been demonstrated. There have been a few clinical trials targeting tau and microtubule dysfunction, although none have had any disease modifying effects. Understanding tau biology is critical to the development of pharmacologic agents that could have disease modifying effects on the primary tauopathies.

INTRODUCTION

Tauopathy is an umbrella term that subsumes many different entities, all characterized by the abnormal deposition of tau in the brain.[1–3] Many entities subsumed under the umbrella term tauopathy are diseases that can have varying clinical presentations, some of which can overlap between diseases, resulting in a complex web of clinical syndromes and tauopathy associated diseases. Some primary tauopathies do not have a clinically defined presentation, and some are considered age-related. Table 1 is a list of age related tauopathies and disease

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that are currently considered primary tauopathies. For those considered diseases, the abnormal tau is thought to account for the primary underlying neurodegenerative process. All diseases that are considered primary tauopathies have in common the abnormal deposition of aggregated tau in the brain. There are other diseases, in which tau deposition can be observed, but for one reason or another, tau either co-exists with another protein, or tau is not considered the primary neurodegenerative process. Diseases in this latter category include: Alzheimer's disease in which beta-amyloid is also present,[4, 5] Lewy body disease in which alpha-synuclein is also present,[6] myotonic dystrophy,[7] subacute sclerosing panencephalitis,[7] Down's syndrome,[8] and Niemann-Pick disease-type C.[7] Tau can be detected at autopsy with immunohistochemical techniques that utilize specific antibodies that recognize different epitopes of tau. One of the most recent advances in the field has been the development of radioligands that can detect tau in the brain in-vivo via positron emission tomography. In this review, I will discuss tau biology, clinical and pathological diagnosis of the primary tauopathies, and recent advances in research related to the primary tauopathies.

TAU BIOLOGY

Tau is encoded by the microtubule-associated protein, tau gene, which is located on chromosome 17q21.[9, 10] Tau is a microtubule-associated protein that functions in the stabilization and assembly of microtubules[11]. Microtubules are important for axonal transport and for maintaining the structural integrity of the cell. In the adult brain, tau is located within neurons, predominantly within axons.[12] Tau is also found in oligodendrocytes and astrocytes where its function is similar to its function in neurons.[13, 14] The tau amino acid sequence can essentially be divided into four compartments: the N-terminal domain, a proline rich domain, a microtubule binding domain, and the C-terminal domain[2]. The N-terminal domain is important to provide spacing between the microtubules. The proline rich domain is important in cell signaling and interactions with protein kinases. The microtubule binding domain is important for binding to the microtubule. The C terminal domain is important in regulating microtubule polymerization. The binding of tau to the microtubule is extremely important. In fact, binding can induce tau conformational change.[15] In its normal form, tau is unfolded and phosphorylated while its abnormal form, found in the brains of patients with primary tauopathies, is characterized by hyperphosphorylated and aggregated tau that has a beta-pleated sheet conformation.[16, 17] The binding of tau to microtubules is regulated by the phosphorylation/dephosphorylation equilibrium of tau.[18] It is currently thought that hyperphosphorylation of tau results in a loss of tau interaction with microtubules leading to microtubule dysfunction and impaired axonal transport, and to tau fibrillarization. Recently, it has been suggested that the primary problem with hyperphosphorylated tau results from an increase in the proportion of tau sequences that are phosphorylated, as opposed to an increase in the number of phosphorylated epitopes on each tau sequence.[19]

Not all tau sequences are created equal. There are six isoforms of tau that are expressed in the adult brain.[20] These six isoforms are derived from alternative splicing of three N-terminal exons in the tau gene: exon 2, exon 3 and exon 10.[20] Three of the six isoforms are due to the splicing in of exon 10, while the other three isoforms are a result of the splicing

out of exon 10. The splicing in of exon 10 results in isoforms with four repeated microtubule binding domains, while the splicing out of exon 10 results in isoforms with thee repeated microtubule binding domains. This is important, because although the healthy human brain consists of equal amounts of tau with three and four repeated binding domains, some primary tauopathies are characterized by a predominance of isoforms with four repeated binding domains (4R tauopathies), some by a predominance of isoforms with three repeated binding domains (3R tauopathies), and some by an approximately equal mix of isoforms with three and four repeated binding domains (3R + 4R tauopathies) (Table 1).

PATHOLOGICAL DIAGNOSIS OF THE PRIMARY TAUOPATHIES

The pathological diagnosis of a primary tauopathy is complex. It not only depends on the immunohistochemical demonstration of abnormal tau deposition in the brain, but also on the presence/absence and amount of other non-tau proteins in the brain, the distribution of the abnormal tau that is deposited, and the morphological characteristics of the tau in different regions of the brain. Further, diagnosis may also depend on the predominant tau isoform that is present, although this is not always straightforward. For example, Pick disease is typically thought of as a 3R primary tauopathy because neuronal tau in Pick disease is primarily 3R tau.[21] However, glial pathology in Pick disease is predominantly 4R tau.[22] Hence, one has to be careful when sampling tissue for biochemical tau analyses for diagnosis. It should also be stressed that although we consider these diseases to be primary tauopathies, in most instances there are pathologies present in addition to the primary tau pathology. In some instances, three or more pathologies may co-exist. It is not uncommon, for example, to have a primary tauopathy such as progressive supranuclear palsy or primary age related tauopathy[23] co-existing with argyrophilic grains disease, another tauopathy.[24] In some instances there may also be beta-amyloid deposition in addition to the primary tauopathy which may not necessarily signify Alzheimer’s disease. Furthermore, protein pathology may also be accompanied by vascular pathology. It is, therefore, not surprising that the clinical phenotypes do not always match perfectly with what one expects based on pathological diagnosis which tends to focus on the so-called, “leading pathology”.

AGE RELATED TAUOPATHIES

Before discussing diseases that are considered primary tauopathies, it is worth mentioning that the presence of tau and hence a tauopathy is not always considered a disease process. Three age related tauopathy are worth further discussion: argyrophilic grain disease; primary age-related tauopathy and aging related tau astrogliopathy. Argyrophilic grain disease as the name implies indicates that its presence is not normal or solely due to aging. Argyrophilic grain disease is characterized by the presence of silver positive grain like structures identified primarily in the medial temporal lobe. To date, there is no definitive clinical feature associated with the presence of this pathology. Hence, it remains to determine whether argyrophilic grain disease is truly a neurodegenerative disease. The term primary age-related tauopathy was recently coined.[23] It refers to the presence of tau deposition in neurons within limbic structures of the brain, in the absence of, or minimally present, beta-amyloid deposition. Primary age-related tauopathy is considered by most, although not all, distinct from Alzheimer’s disease. Recently it was demonstrated that primary age-related

tauopathy is associated with subtle cognitive slowing and executive dysfunction, as well as atrophy of the left anterior hippocampus.[25] Hence it appears that this pathology may not truly be indicative of tau deposition solely from normal aging. Unlike primary age-related tauopathy in which tau is deposited in neurons, aging related tau astrogliopathy is characterized by tau deposition in astrocytes. Currently, there is no clinical correlate of aging related tau astrogliopathy.

CLINICAL DIAGNOSIS OF DISEASES CONSIDERED PRIMARY TAUOPATHIES

Without specific biomarkers, it is difficult to make a diagnosis that is 100% predictive of an underlying tauopathy. Table 2 is a list of common presenting signs and symptoms and whether their presence is suggestive of an underlying tauopathy. As can be seen, most signs and symptoms by themselves are not going to be helpful in predicting an underlying tauopathy with any degree of certainty. Instead, it has become clear that recognition of a profile, or constellation of signs and symptoms, is more helpful than linking a specific sign or symptom, in predicting an underlying tauopathy. This profile or constellation of signs and symptoms is better known as a syndrome. Hence, in order to best predict an underlying tauopathy, in the absence of a specific biomarker, we have now come to rely on the recognition of specific syndromes that are highly suggestive of a tauopathy. The following three syndromes are highly suggestive of, although not pathognomonic for a tauopathy diagnosis: Richardson's syndrome; primary progressive apraxia of speech; and corticobasal syndrome.

Richardson's syndrome

Richardson's syndrome is the classic presenting syndrome suggestive of a pathological diagnosis of progressive supranuclear palsy,[26] and hence suggestive of an underlying primary tauopathy. This syndrome is characterized by the insidious onset and progression of gait and balance problems leading to unexplained falls. Typically, patients with Richardson's syndrome will have additional symptoms present at onset including sensitivity to bright light, dizziness, a hoarse raspy voice, neck stiffness, an unusual facial appearance with the eye brows elevated, and a general slowing down of movements. Patients may be described as having a loss of general interest in people about them or apathy. A resting tremor and loss of memory are not present arguing against a diagnosis of Parkinson's and Alzheimer's disease, respectively. Neurological examination reveals the presence of executive dysfunction (evidence of disorganization and poor planning) and a relatively symmetric akinetic rigid syndrome. There is a loss of postural reflexes, axial rigidity (neck and trunk rigidity) and loss of, or slowness of, vertical eye movements to commands but relatively preserved eye movements with the dolls eye maneuver (supranuclear gaze palsy). Treatment with high doses of carbidopa/levodopa (> 600mg) and similar agents are typically unhelpful with an absence of any clinically significant response.

Primary progressive apraxia of speech

Primary progressive apraxia of speech is also characterized by an insidious onset and worsening of symptoms over time.[27] The main clinical features are a slow effortful speech

sometimes associated with difficulty articulating words, leading to the production of either distorted sounds or the substitution of normal sounds with distorted sounds or speech output with lengthened intersegment durations between syllables, words, or phrases.[28] Sometimes one may observe groping movements of the tongue and mouth, and multiple trials in order to produce the intended sounds. Currently, two variants of primary progressive apraxia of speech are recognized: a phonetic variant in which articulatory errors dominate (Type 1) and a prosodic variant in which a slowed speech output is typical (Type 2).[29] Language characteristics including syntax, grammar, comprehension, and naming are intact. Hence, the patient easily understands spoken and written sentences and word meaning. Over time primary progressive apraxia of speech evolves and after 6–7 years many patients develop features that begin to look more like Richardson's syndrome.[30] In other patients aphasia develops and progressively gets worse in the absence of features typical of Richardson's syndrome. Regardless, eventually all patients with primary progressive apraxia of speech become mute, although communication by other means such as writing, gesticulating, typing, texting or signing remains in intact.

Corticobasal syndrome

The corticobasal syndrome is the third syndrome that is also strongly associated with an underlying tauopathy,[31] although of all the three syndromes discussed it may be the least specific to an underlying primary tauopathy.[1, 32] The corticobasal syndrome is characterized by the presence of asymmetric clinical features that suggest a combination of cortical and subcortical (basal ganglia) pathology. Cortical dysfunction can manifest as the alien limb phenomenon[33] (in which the patient has lost control over a limb) attributed to involvement of sensory motor cortices and connections. Patients may personify their limb and sometimes will refer to their limb as "my little friend". Another typical feature is the presence of limb apraxia in which the patient may not be able to perform a task that previously could be performed in the absence of motor weakness. For example, a patient may not know how to use a screw driver to drive a screw having done so for decades before. Some patients may manifest unwanted movements of other body parts (e.g. opening and closing of the mouth with alternating movements of the hand) and may have cortical sensory loss and agraphesthesia (difficulty recognizing a number or a letter that is traced in the palm of the hand). Myoclonus (quick involuntary jerks) and dystonia (abnormal posturing) may be observed. Basal ganglia related features must also be present, and may include asymmetric limb rigidity and/or akinesia (decreased speed of movement), with little significant or sustained improvement from levodopa therapy. Although not always present, cortical dysfunction of the frontal and temporal lobes may manifest as executive dysfunction, behavioral or personality change, or aphasia (language impairment).

Other clinical features and syndromes

Other clinical syndromes can also be associated with a primary tauopathy. However, many of these other clinical syndromes are less specific and hence are equally likely, or even more likely, to be associated with another neurodegenerative process in which tau is not consider the primary problem. These include the behavioral variant of frontotemporal dementia (in which patients present with behavioral and personality change)[34], the logopenic variant of primary progressive aphasia (in which patients present with language and other problems

affecting naming, word retrieval, working memory and calculations)[35] and semantic dementia (in which patients present with a loss of object knowledge, for example not knowing that a zebra has stripes or that a carrot is orange in color).[36] Other classic clinical syndromes such as dementia with Lewy bodies (in which dementia, Parkinsonism and psychoses occur in any combination)[6] are rarely associated with a primary tauopathy. One clinical feature that merits further discussion is that of head trauma. Chronic head trauma has been associated with the primary tauopathy, chronic traumatic encephalopathy. This pathology was recently characterized as the accumulation of abnormal tau in neurons and glial cells that are located predominantly around small blood vessels at the depths of cortical sulci and in an irregular pattern.[37] Currently there are many unanswered question regarding chronic traumatic encephalopathy, and other than head injury “at some point in time”, there is little clinical data associated with this primary tauopathy.

CLINICALLY AVAILABLE DIAGNOSTIC TESTS

At the present time, there is no clinically available test that is specific to an underlying tauopathy. There are, however, some tests that may be more suggestive of any underlying tauopathy than others that are worth discussing. There are no blood tests that can determine whether a patient has an underlying tauopathy or not. Some studies have suggested that measuring tau levels, total tau levels and phosphorylated tau levels in cerebrospinal fluid may provide support for an underlying tauopathy[38]. Others report no association between cerebrospinal fluid tau levels and the presence or absence of an underlying tauopathy[39].

Neuroimaging modalities on-the-other-hand may provide some help when considering a diagnosis of a tauopathy. There are a handful of clinically useful findings on magnetic resonance imaging (MRI) and on molecular imaging that although not specific, can provide some help in making a diagnosis of a tauopathy. MRI head scan is typically performed to exclude the presence of structural lesions that could account for presenting syndromes suggestive of an underlying tauopathy. However, MRI also reveals anatomic patterns of involvement that are somewhat useful for diagnosing a tauopathy. One such feature is the presence of midbrain atrophy, particularly in the absence of atrophy of the pons,[40, 41] although this is not a sensitive marker of pathology[42]. This is sometimes referred to as the hummingbird sign due to a reduction in the anterior-posterior diameter of the midbrain[43] (Figure 1). Atrophy, seen as flattening of the superior colliculi, and atrophy of the superior cerebellar peduncles[44, 45] are also strongly associated with, and hence suggestive of, the presence of an underlying tauopathy. Striking atrophy (referred to as knife edge atrophy) of the frontal and temporal lobes on MRI (Figure 1) can be a feature of Pick disease,[46] and hence when this characteristic pattern of atrophy is present it is suggestive of an underlying 3R tauopathy. Asymmetric frontoparietal atrophy (Figure 1) is somewhat suggestive of underlying corticobasal degeneration pathology. In addition to MRI, [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) may also provide clues to the presence of an underlying tauopathy.[47] Atrophy of the midbrain results in a focal signal of hypometabolism in the midbrain (Figure 2) known as the pimple sign.[48] In addition, sometimes there is a subtle hypometabolic track between the midbrain and the cerebellum, likely reflecting atrophy of the superior cerebellar peduncles that may also be present (Figure 2). Other features suggestive of an underlying tauopathy include focal

hypometabolism of the lateral premotor and supplementary motor cortices[47] (Figure 2), as well as frontoparietal and caudate hypometabolism occurring together[49] (Figure 2). It must be pointed out, however, that all of the abnormalities discussed relating to MRI or FDG-PET are less than 100% sensitive and specific for diagnosing an underlying primary tauopathy.

MANAGEMENT OF TAUOPATHIES

At present there are no disease modifying therapies for treating tauopathies. Treatment of tauopathies focuses on alleviating or ameliorating symptoms for which treatment exists. Unfortunately, many symptoms and signs albeit debilitating are untreatable. Medications are ineffective to ameliorate Parkinsonism and hence patients do not typically respond to dopamine targeted treatments. Management is complex, however, and one has to target whatever symptom is most bothersome to the patient and their careers. For example, a patient with an underlying tauopathy and a Richardson syndrome presentation may be most bothered by bright lights (photosensitivity).[50] Management would simply be having the patient wear dark sun glasses that prevent exposure to bright light. Hence, management for photosensitivity is not specific to photosensitivity in tauopathies but photosensitivity in general. Since almost any symptom can be associated with an underlying tauopathy detailed and specific management of each and every symptom and sign is beyond the scope of this review. Table 3 provides a list of symptoms commonly observed in the primary tauopathy and general guidance on management of such symptoms. Some symptoms that are typically encountered in tauopathies that may respond relatively well to pharmacologic treatments include depression, anxiety, myoclonus, pathological crying/laughing, and insomnia. Others, including vertigo, diplopia (double vision), dystonia, Parkinsonism, poor appetite and weight loss, are difficult to treat and may not respond to any available treatment. There are also non-pharmacologic options that should be offered to patients with suspected tauopathy.[51] Physical therapy for gait and balance problems is useful to prevent a faster decline in motor function but will not reverse any loss of function. Speech therapy is helpful in patients with progressive apraxia of speech and a swallow evaluation is critical any patient who is having trouble swallowing. A simple maneuver such as tucking the chin when swallowing can help reduce the risk of aspiration. Patients who are mute can benefit from the usage of devices that allow for communication in the absence of marked to severe aphasia or motor dysfunction of the limbs which typically can occur later in the disease course.

GENETIC FACTORS

There is some evidence that the primary tauopathies may have genetic links. The chromosomal region containing the microtubule associated protein tau gene includes two major haplotypes, H1 and H2, which are essentially defined by linkage disequilibrium between several polymorphisms over the entirety of the gene.[52] The inheritance of the H1 haplotype and the H1/H1 genotype in the western world is a risk factor for the development of a primary tauopathy.[52, 53] Linkage disequilibrium fine -mapping analysis has also further demonstrated an association between the primary tauopathies and the microtubule associated protein tau H1c haplotype, which is a variant of the H1 haplotype.[54, 55] This variant has been shown to be associated with increased deposition of the 4R tau isoforms.[54–56] Interestingly, the H2 haplotype has been suggested to be associated with a protective effect against the

development of a primary tauopathy.[57] A large genome wide association study of the primary tauopathy progressive supranuclear palsy discovered previously unidentified signals associated with progressive supranuclear palsy,[58] although none have been subsequently shown to have any relevance.

RECENT ADVANCES IN TAU RESEARCH

Tau-PET

The determination of whether a patient has one of the primary tauopathies or not typically occurs at the time of autopsy after the patient has dies. Recently, however, there has been the development of in-vivo PET radiotracers that allows for the detection of tau in the brain in vivo. Previously, there were only tracers that allowed for the in-vivo detection of beta-amyloid.[59] Over the past 5-years there have been many radiotracers developed with the intention of selectively detecting tau in the brain[60]. Unfortunately, due to many unwanted side-effects and other problems with these tracers such as toxic metabolites, many of these tracers have not been successfully translated into research. Of the tracers that have been tested, one tracer that has been very successfully integrated into research is [18F]AV-1451.[61, 62] Autoradiographic studies have demonstrated that [18F]AV-1451 selectively binds to tau, does not bind to other proteins such as beta-amyloid, alpha-synuclein and others, and is safe for human studies.[61, 63–65] Many studies have now demonstrated that AV-1451 can detect 3R+ 4R tau isoforms and hence is a very good biomarker to study Alzheimer's disease which is characterized by the presence of 3R+4R tau.[66, 67] Unfortunately, AV-1451 does not look as promising to detect isolated 3R, or 4R tau. There is relatively little observed binding to tau in the primary tauopathies, compared to Alzheimer's disease[49, 68–70] (Figure 3). Furthermore, there appears to be off target binding in the basal ganglia, midbrain and elsewhere, with AV-1451, regions that are critically involved in 4R tauopathies[63, 65] (Figure 3). Therefore, AV-1451 may not be a good biomarker for the primary tauopathies. Two other tau tracers have also been utilized in research. Unfortunately, none of them have proven to be superior to AV-1451 for studying the primary tauopathies. With-that-said, PBB3, may have the ability to detect a wider range of the primary tauopathies due to more robust binding to 4R tau isoforms[71]. The second, THK5351, has also been performed in patients suspected of having an underlying primary tauopathy with similar results to AV-1451[72] although binding may be targeting dopamine related receptors and not tau?

Prion-like properties and propagation of tau

Over the past decade one area of tau research that has dominated the field, is whether tau has prion like properties and can propagate from cell to cell and beyond.[73, 74] More specifically, does tau behave like a prion and can it be transmitted like an infection. The term prion was first coined by Prusiner in 1982 to describe the infectious transmissibility of a proteinatious particle.[75] The concept of tau being prion-like may date back to the idea that tau, in the form of neurofibrillary tangles, has a stereotypic pattern of spread throughout the brain in Alzheimer's disease when the Braak staging scheme was published.[4] This staging scheme, although developed from cross-sectional analysis, suggests that tau first deposits in the transentorhinal cortex before spreading to the hippocampus proper and then multimodal and

unimodal cortices. Adding fuel to the fire was the demonstration that hyperphosphorylated tau could recruit or seed normal tau to assemble into filamentous aggregates.[76] More recently, three important areas of study have been published that further promotes this idea. The first provided some evidence that extracellular tau may be able to enter cells and promote tau aggregation inside the cell.[77] The second was the demonstration that tau when injected into mice may promote tau filamentous aggregation.[78] The third provided some evidence that tau can jump from cell to cell.[79] This notion of prion-like behavior of tau is very contentious however, given the lack of transmission like an infection, with many researchers opposing the notion that the behavior of tau mirrors that of the prion proteins of spongiform encephalopathy.[80]

TREATMENT TRIALS AND FUTURE DIRECTIONS

There are many different approaches being directed at treating tauopathies. These approaches include stabilizing microtubules, decreasing hyperphosphorylated tau, inhibiting protein kinases, inhibiting aggregation of tau fibrils, and enhancing intracellular tau degradation. Four different agents have been tested so far in human Phase I–III trials including methylene blue, riluzole,[81] the octapeptide NAP,[82] and tideglusib.[83] None of these compounds have shown any evidence for efficacy. In addition, many different tau immunotherapies are currently being assessed[84]. Such immunotherapies involve both active and passive vaccine approaches with antibodies being developed that targets full-length tau, tau fragments or specific epitopes of tau.[84]

Two areas of active tauopathy research that will likely define the near future are the continued development of biomarkers that can detect in-vivo tau, and the development of compounds or antibodies for clinical trials that target tau. In addition, one would expect the continued development of mouse models to better represent the primary tauopathies and genetic studies to identify genetic influences that either account for disease or provide a model to study disease. Most of these research endeavors will likely focus on Alzheimer's disease given the higher prevalence of this disease, growing elderly population, heightened awareness, financial burden to society and potential financial gains associated with discoveries, although there is some research that is now focused on the primary tauopathies, particularly progressive supranuclear palsy. Focusing on the primary tauopathies is critical, as it is unclear whether any biomarker or treatment developed targeting non-primary tauopathies such as Alzheimer's disease will also be equally applicable to the primary tauopathies.

CONCLUSION

The primary tauopathies represent a group of pathological entities in which most, but not all, are considered a type of neurodegenerative disease. All primary tauopathy are associated with the deposition of abnormal hyperphosphorylated tau protein. There are a few clinical features that are highly suggestive of an underlying primary tauopathy but there are no perfect clinical or neuroimaging biomarkers that are able to accurately, and robustly, detect and differentiate the different types of primary tauopathies. Basic research related to the primary tauopathies include mouse and fly models, as well as studies at the cellular level

with some researchers suggesting tauopathies are prion-like diseases. At present there are no disease modifying treatments, although clinical trials have begun to focus more on the primary tauopathies.

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LIST OF ABBRVIATIONS

3R	tau isoform with 3 repeats in the microtubule binding domain
4R	tau isoform with 4 repeats in the microtubule binding domain
3R + 4R	mixed 3 and 4 repeat tau isoforms
AV-1451	a type of ligand that selectively binds to tau
FDG-PET	fleurodeoxyglucose positron emission tomography
MRI	magnetic resonance imaging
PBB3	a type of ligand that selectively binds to tau
THK5351	a type of ligand that selectively binds to tau

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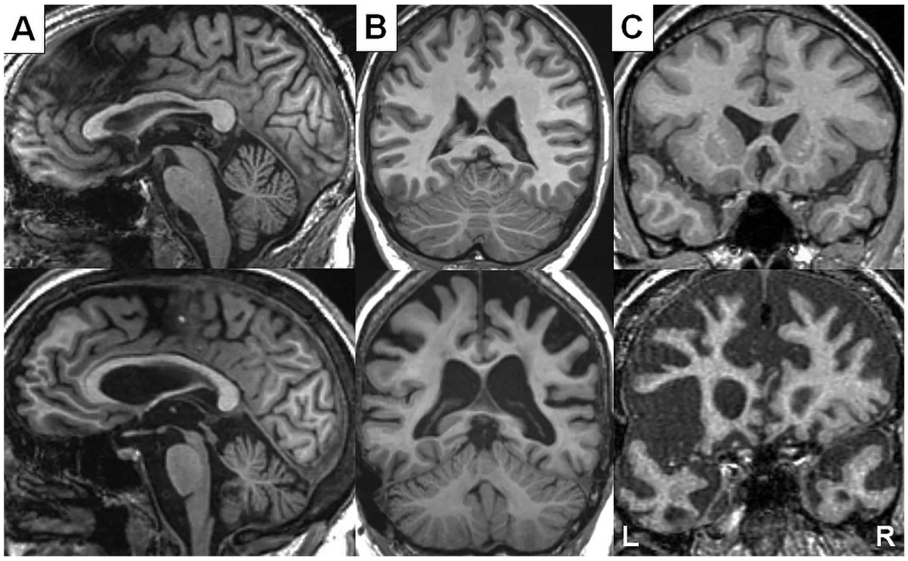

Figure 1.

T1 weighted MRI features suggestive of an underlying primary tauopathy include the humming bird sign resulting from atrophy of the dorsal midbrain and preserved pons (A, bottom image) suggestive of progressive supranuclear palsy, asymmetric parietal atrophy, right greater than left, suggestive of corticobasal degeneration (B, bottom image) and striking atrophy of the prefrontal cortex and anterior temporal lobe with secondary ventricular enlargement, worse of the left (C, bottom image) suggestive of Pick's disease. Top images are normal MRI scans for comparison.

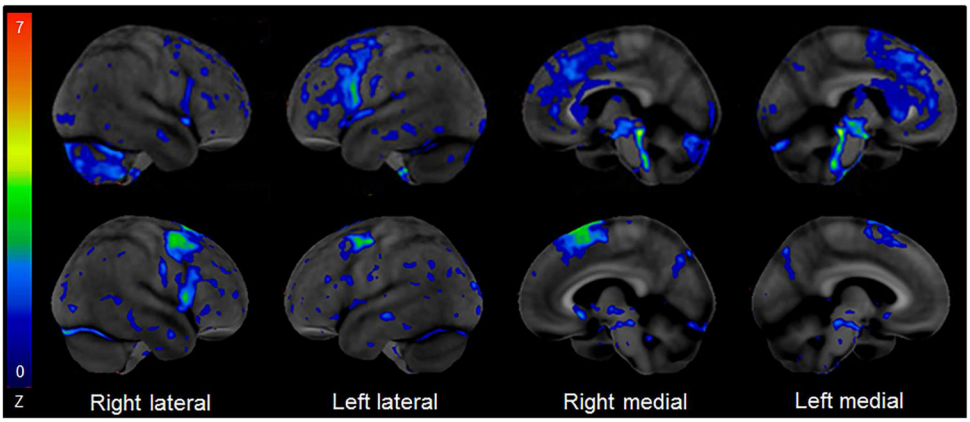

Figure 2.

[18F] Fluorodeoxyglucose PET scan using the Cortex Suite software reveals mild hypometabolism of the left posterior frontal cortex, bilateral supplemental motor cortices, midbrain, superior cerebellar peduncle and right cerebellum in a case of Richardson's syndrome (top row) and mild hypometabolism in bilateral posterior frontal cortices, and right supplemental motor cortex in a patient with primary progressive apraxia of speech (bottom row) suggestive of an underlying primary tauopathy.

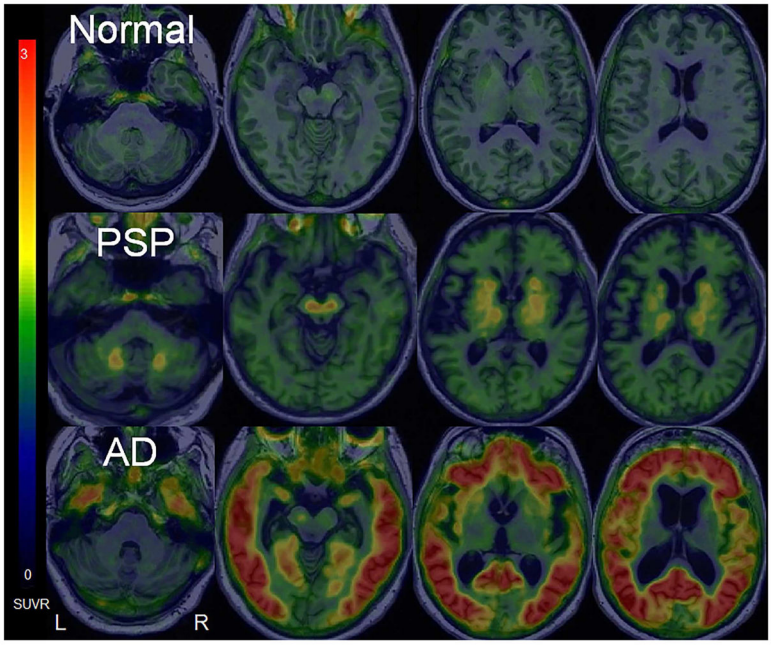

Figure 3.

[18F] AV-1451 tau-PET shows minimal uptake in a normal control patient (top row), mild-moderate uptake in the dentate nucleus of the cerebellum, midbrain and basal ganglia in a patient with progressive supranuclear palsy (PSP), a primary 4R tauopathy (2nd row), and striking uptake in the cortex in a patient with typical Alzheimer's disease (AD), a 3R + 4R tauopathy, for comparison (bottom row).

Table 1

List of entities considered primary tauopathies

Current pathological diagnoses	Type of tauopathy
Pick's disease	3R tauopathy
Progressive supranuclear palsy	4R tauopathy
Corticobasal degeneration	4R tauopathy
Argyrophilic grain disease	4R tauopathy
Globular glial tauopathies	4R tauopathy
Aging-related tau astrogliopathy	4R tauopathy
Chronic traumatic encephalopathy	3R+4R tauopathy
[a] Primary age-related tauopathy (PART)	3R+4R tauopathy
Parkinsonism-Dementia complex of Guam	3R+4R tauopathy
Postencephalitic Parkinsonism	3R+4R tauopathy
Atypical Parkinsonism of Guadeloupe	3R+4R tauopathy
Diffuse neurofilament tangles with calcification	3R+4R tauopathy
Frontotemporal dementia & Parkinsonism liked to Chromosome 17	3R, 4R, or 3R+4R tauopathy

[a]This diagnosis now includes the entity previously known as tangle dominant dementia

Table 2

List of clinical signs and symptoms and their association with an underlying tauopathy

Specific signs and symptoms	Association with tauopathy
Motor	
Vertical supranuclear gaze palsy	+
Axial rigidity	+
Unexplained falls	+
Speech apraxia	+
Limb apraxia	±
Dysarthria	±
Stiffness of muscles	±
Dystonia	±
Action myoclonus	±
Early gait freezing (freezing while trying to walk)	±
Resting tremor	−
Ataxia	−
Weakness of limb	−
Cognitive & Behavioral	
Memory loss	±
Behavioral and/or personality change	±
Limb apraxia	±
Spatial/perceptual deficits[a]	−
Aphasia in the absence of speech apraxia	−
Problems with calculations	−
Loss of word or object knowledge	−
Loss of facial recognition	−
Other	
Depression/Anxiety	±
Head trauma	±
Constipation	±
Loss of smell	±
Urinary incontinence	±
Orthostatic hypotension	−
Fasciculation	−
Rapid eye movement sleep behavior disorder	−
Delusions (e.g. Capgras, Othello's)	−
Visual/auditory/tactile hallucinations	−

+ Highly suggestive of underlying primary tauopathy, ± Equivocal; −argues against underlying primary tauopathy

[a]Only rarely associated with a primary tauopathy

Table 3

Symptoms that commonly occur in the primary tauopathies and associated management likely to provide some benefit

Symptoms	**Management**
Postural tremor	Beta-blockers
Slowness of movements	Dopamine
Muscle stiffness	Dopamine
Sensitivity to bright lights	Wearing dark sunshades
Involuntary eye closure	Botox
Neck pain associated with dystonia	Botox
Drooling	Botox of salivary glands
Trouble with balance and falls	Physical and occupational therapy
Trouble swallowing	Swallow evaluation
Choking while eating or drinking	Swallow evaluation
Dysarthria or apraxia of speech	Speech therapy
Excessive tearing (lacrimation)	Artificial tears multiple times daily
Difficulty falling or staying asleep	Proper sleep hygiene, behavioral and pharmacologic management
Excessive daytime sleepiness	Caffeine, proper sleep hygiene
Depression	Antidepressants
Anxiety	Anxiolytics
Emotional incontinence (laughs/cries excessively)	Antidepressants and Nuedexta
Loss of sex drive (libido)	Exercise, antidepressants