Chapter 13

The Tauopathies

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Abstract

Tauopathies are a clinically and neuropathologically heterogeneous group of neurodegenerative disorders, characterized by abnormal tau aggregates. Tau, a microtubule associated protein, is important for cytoskeletal structure and intracellular transport. Aberrant post-translational modification of tau results in abnormal tau aggregates causing neurodegeneration. Tauopathies may be primary, or secondary, where a second protein, such as Aß, is necessary for pathology, as in Alzheimer's disease, the most common tauopathy. Primary tauopathies are classified by tau isoform and cell types where pathology predominates. Primary tauopathies include Pick disease, corticobasal degeneration, progressive supranuclear palsy and argyrophilic grain disease. Environmental tauopathies include chronic traumatic encephalopathy and geographically isolated tauopathies such as Guam-Parkinsonian-dementia complex. The clinical presentation of tauopathies vary based on the brain areas affected, generally presenting with a combination of cognitive and motor symptoms either earlier or later in the disease course. As symptoms overlap and tauopathies such as Alzheimer disease and argyrophilic grain disease often coexist, accurate clinical diagnosis is challenging when biomarkers are unavailable. Available treatments target cognitive, motor, and behavioral symptoms. Disease modifying therapies have been the focus of drug development, particularly agents targeting Aß and tau pathology in Alzheimer disease, although most of these trials have failed.

Key words: tauopathy review pathology diagnosis treatment Alzheimer Pick Corticobasal degeneration

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Introduction

Tauopathies are neurodegenerative diseases that are pathologically characterized by abnormal tau aggregates in neurons and glial cells. They are responsible for the majority of dementias worldwide, including Alzheimer's disease (AD). Despite sharing pathological tau aggregation, tauopathies exhibit tremendous clinical and phenotypic heterogeneity, associated with variability in the predominant tau isoforms that aggregate, morphology of aggregates, cell types, and brain regions affected (Chung et al., 2021). Additionally, morphologies of tau inclusions can be different even within the same cell type, suggesting distinct mechanisms in each tauopathy.

Pure tauopathies are a rarity, as most coexist with each other, and with other neurodegenerative pathology. For instance, argyrophilic grain disease, an under-recognized tauopathy, is present in 18-100% of cases of progressive supranuclear palsy and corticobasal degeneration, and in up to a quarter of patients with AD (Yokota et al., 2018). In an autopsy series of cases meeting neuropathological criteria for AD, less than a third had AD-only pathology, and even within this group, nearly a half had at least one infarct (Karanth et al., 2020). Because of the overlap of clinical syndromes between tauopathies, the positive predictive value of even an expert clinical diagnosis of AD, prior to the advent of biomarkers, ranged from 62-83% (Beach et al., 2012).

Primary tauopathies arise from abnormal tau aggregates within neuronal or glial cells or in both cell types. Alzheimer's is the prototypical secondary tauopathy, where a second protein, Aß, is needed to drive neurodegeneration. In AD, tau aggregates are seen only in neurons and not in glial cells. Environmental tauopathies are primary tauopathies and include geographically isolated tauopathies and chronic traumatic encephalopathy.

This review covers the structure and function of normal tau, the types of pathological tau, and describe salient clinical and pathologic characteristics of the major primary, secondary, and environmental tauopathies. We will discuss the challenges of both clinical and pathological diagnosis of tauopathies. Finally, we will

address available, generally symptomatic treatments for these disorders, as well as disease modifying drugs in development, primarily for Alzheimer's disease.

Structure and function

Normal Tau

Microtubules are tubulin polymers that are necessary for cell structure and function. Tau- for tubulin associated unit- is one of the most abundant of several microtubule associated proteins (MAP) found in the nervous system. Tau catalyzes microtubule polymerization, promoting cytoskeleton structure and axonal transport (Weingarten, et al., 1975). Other tau physiological functions include signal transduction, DNA/RNA protection, and regulation of synaptic function (Catarina Silva and Haggarty, 2020).

Tau probably has many other undiscovered functions. For instance, tau exists in forms that do not associate with microtubules and interacts with many other proteins besides microtubules in tissue compartments outside the central nervous system (Lee and Leugers, 2012). Interestingly, tau is present in muscle, liver, and kidney tissue, and in human breast, prostate, gastric, and pancreatic cancer cell lines. The tau sequence is conserved across species, including mammals, amphibians, and nematodes (Lee and Leugers, 2012). In the brain, tau is present in neurons, primarily in axons and dendritic processes, but also in astrocytes and oligodendrocytes.

In its native state, tau is unfolded and disordered, lacking a well-defined structure, and poised for rapid conformational change, with the majority of tau proteins interacting with neuronal microtubules. However, this very property of structural plasticity also makes tau much more likely to misfold (Kolarova et al., 2012; Catarina Silva and Haggarty, 2020). Native tau is highly soluble, contains several charged and hydrophilic residues, and shows little tendency for aggregation. Fast single-molecule tracking of tau in living neurons shows tau binding to a microtubule for ~40 ms, before moving to the next microtubule in a "kiss-and-hop" fashion, a technique that allows tau to modulate tubulin-microtubule balance and promote microtubule assembly, without interfering with axonal transport (Janning et al., 2014).

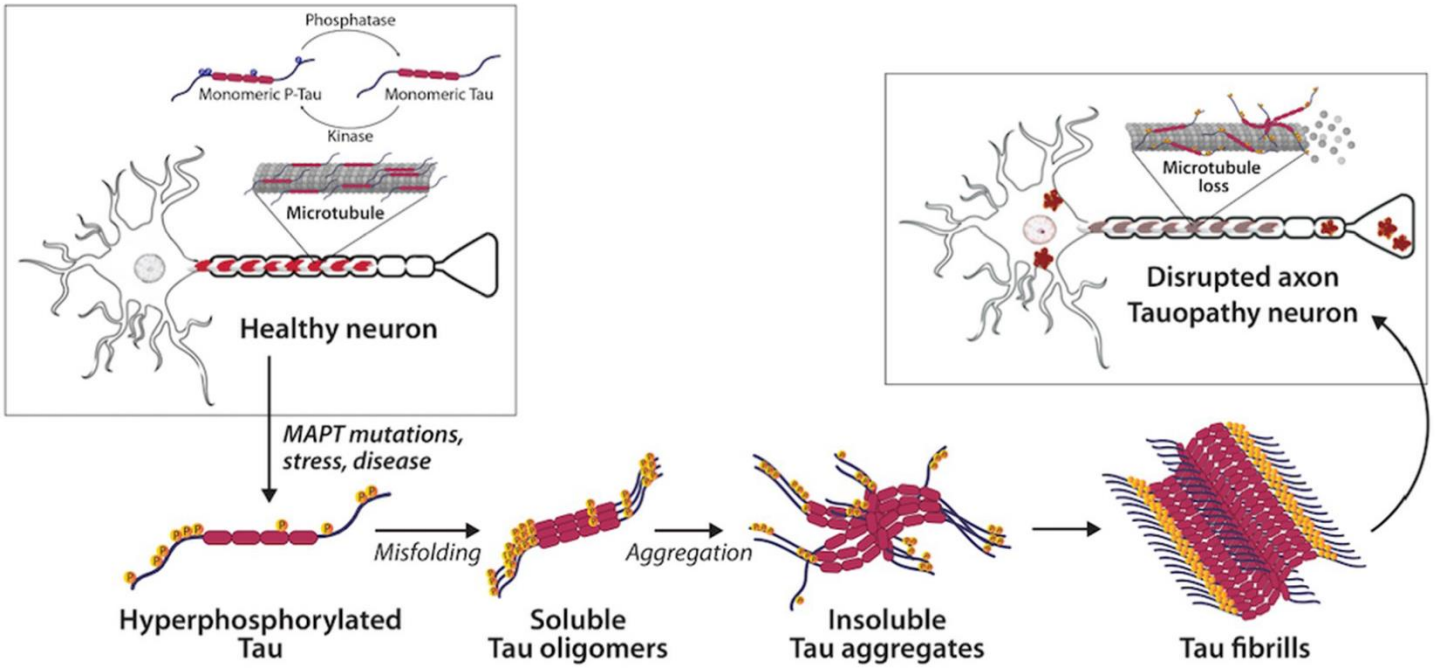
Six isoforms of tau are derived from differential splicing of exons of the microtubule associated protein tau (MAPT) gene on chromosome 17q21 (Neve et al., 1986). Tau has an amino (N) and carboxyl (C) terminal end, a central protein rich domain, and a repeat domain, with either three or four repeats (3R or 4R) and differing number of N-terminal inserts (0 N, 1 N or 2 N) from differential splicing of exons of the MAPT gene yielding the six tau isoforms. The repeat domains are crucial for regulating microtubule stability and axonal transport. Therefore, during the fetal stage, 3R tau predominates, with dynamic properties promoting synaptogenesis and neural network formation, while in the adult brain 4R tau binds more tightly to microtubules (Goedert, 2011; Goedert et al., 1989). Full-length tau has 2 N terminal inserts and 4R repeats and it is referred to as "2N4R" tau. The dominant forms found in human brain are 2N4R and 2N3R. Under physiological conditions, there are equal amounts of 3R and 4R. In pathological conditions, there is a shift to the 2N4R configuration for most tauopathies.

Pathological Tau

The psychiatrist Alois Alzheimer first described aggregated tau in terms of neurofibrillary tangles (NFT) in 1906 in the eponymous dementia named for him by his department chairman, Emil Kraepelin (Devi and Quitschke, 1999). Nearly sixty years later, paired helical filaments (PHFs) were described as a major component of NFTs (Kidd, 1963). In 1975, the tau protein was isolated (Weingarten et al., 1975), and the following decade tau was found to be the component of NFTs in 1985 (Brion et al., 1985; Grundke-Iqbal et al., 1986; Kosik et al., 1986). In its inherently disordered state, the tau protein is the most common misfolded protein. Site-specific hyperphosphorylation of tau is a hallmark of neurodegenerative tauopathies and common to all diseases with tau filaments, in which neuronal and glial cells exhibit various intracellular tau inclusions. Tau also undergoes other post-translational modifications, such as acetylation, ubiquitination, and cleavage (Chung et al., 2021). These modifications affect tau solubility and tau-microtubule interactions, likely disrupting axonal transport, causing synaptic dysfunction and loss, and leading to neurotoxicity. The abnormal hyperphosphorylation of tau, an early event that appears to precede filament assembly, prevents usual tau interaction with microtubules, and detaches tau from microtubules, causing microtubule breakdown. The

hyperphosphorylated tau then misfolds, oligomerizes, and begins to abnormally aggregate with other aberrantly modified tau proteins, forming insoluble, highly ordered, sheet-rich paired helical filaments (PHF) and NFTs (Kosik et al., 1986) (Figure 1). 4R-tau is more aggregation prone than 3R-tau.

Figure 1

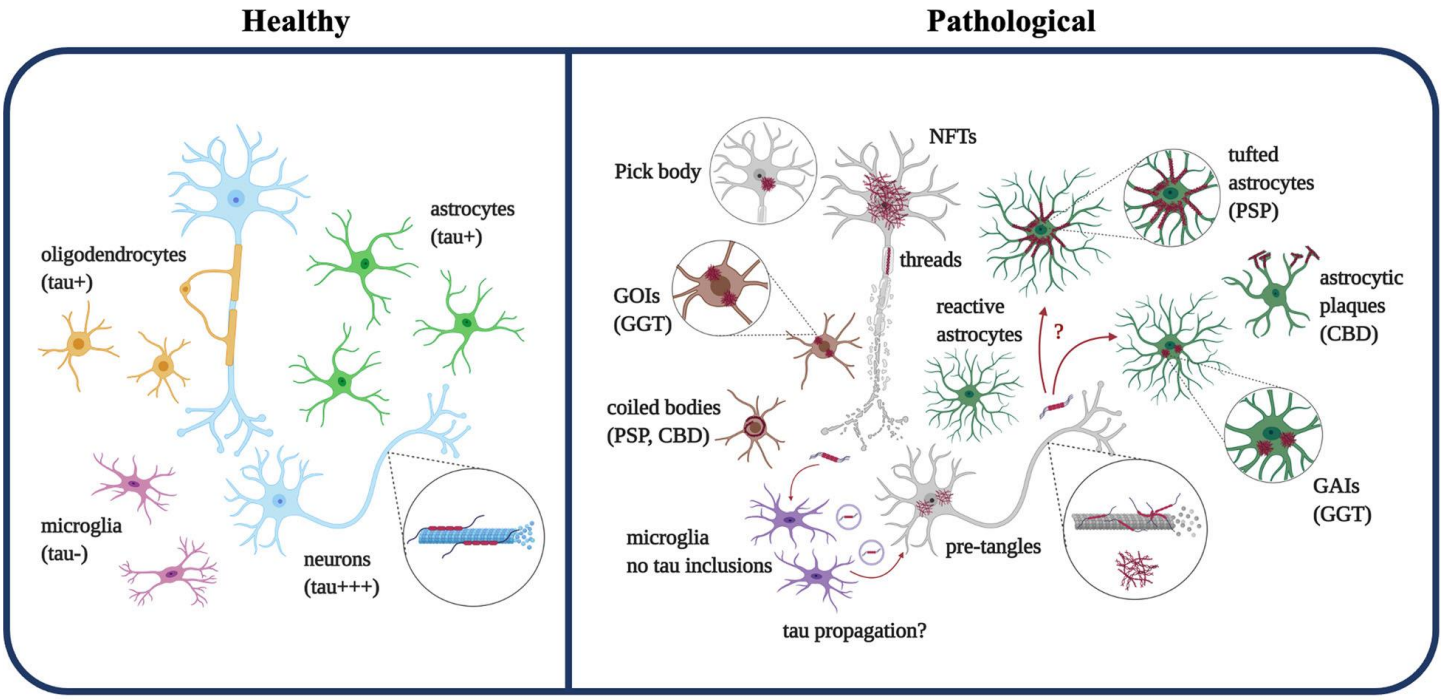


Fast axonal transport is significantly impaired in tauopathies, likely due to alterations in the normal function of tau (Morfini et al., 2009). Effects of tau on axonal transport may be more complex than simply blocking motor access to the microtubules (Lee and Leugers, 2012). Pathologic tau may also act as a seed to promotes aggregation of free, soluble tau(Gibbons et al., 2019). Tau seeds can transmit pathologic tau through intracerebral injection into wild-type or tau transgenic mice of recombinant tau protein, cell lysates of pathological tau strains, or brain tissue derived tau seeds. Human brain-derived tau seeds injected into mouse brains replicate the neuropathologic lesions of the donor brain tauopathies, with identical affected cell types, lesion morphology, and brain regions affected (Chung et al., 2021). Intriguingly, neurons with NFTs may survive decades, suggesting tau aggregates may be protective (Morsch et al., 1999).

Primary Tauopathies

Tau misfolding and aggregation from post translational modification of tau, primarily hyperphosphorylation, are implicated in all tauopathies, including AD. Tauopathies are mostly sporadic although genetic forms of tauopathy subtypes, indistinguishable from the sporadic, are not uncommon. An example is FTLD-17 dementia resulting from MAPT mutations on chromosome 17. Tauopathies may be divided into primary and secondary tauopathies, with an added group of environmental tauopathies. Primary tauopathies are neurodegenerative diseases that result from aberrant tau aggregates. Environmental tauopathies similarly harbor tau aggregates but the aggregates arise from environmental triggers and are found in geographically isolated or at-risk populations. Secondary tauopathies implicate a second protein in the pathogenesis, with AD being the prototype secondary tauopathy with Aß protein as the additional pathological driver. Tauopathies vary based on tau lesion morphology and cell types affected (Figure 2). Motor symptoms exist with all tauopathies. However, depending on region of brain affected, the nature and type of motor disorder as well as time of onset during disease course, is widely variable (Table 1).

Figure 2



Abbreviations: GOIs, Globular oligodendroglial inclusions; GGT, Global glial tauopathy; PSP, Progressive supranuclear palsy; CBD, Corticobasal degeneration; NFTs, Neurofibrillary tangles; GAIs, Globular astroglial inclusions.

Table 1

Tauopathies and Motor Symptoms

Tauopathy Type	**Motor symptoms**	**Time of Onset**
Primary tauopathy:		
FTLD-tau: Pick's disease	Parkinsonism	Late
FTLD-tau: FTDP-17	Parkinsonism	Early
FTLD-tau: Corticobasal degeneration	Asymmetric parkinsonism, limb dystonia, atypical tremor	Early
FTLD-tau: Progressive supranuclear palsy	Ocular apraxia, falls, axial dystonia	Early
FTLD-tau: Globular glial tauopathy	Dysarthria, dysphagia, corticospinal tract findings	Early
Anti-IgLON5 antibodies tauopathy	Hyperreflexia, spasticity, limb weakness	Early
Argyrophilic grain disease	--	--
Primary age-related tauopathy	--	--
Aging-related tau astrogliopathy	Parkinsonism	Early/late
Environmental tauopathies:		
Chronic Traumatic Encephalopathy	Tremors, Parkinsonism, motor neuron features	Early/Late
Parkinsonian dementia complex of Guam	Parkinsonism	Early
Guadeloupean Parkinsonism	Parkinsonism	Early
Toxic Tauopathy, Northern France	Parkinsonism	Early
Secondary Tauopathy: Alzheimer disease	Extrapyramidal syndrome, gait apraxia, myoclonus	Late

Abbreviations: FTLD, frontotemporal lobe dementia; FTDP-17, Frontotemporal dementia with Parkinsonism-17; IgLON5, Immunoglobulin LON Family Member 5

Frontotemporal dementia

Frontotemporal lobar degeneration (FTLD) is the term defining the pathology of the many clinical syndromes subsumed under the term frontotemporal dementia. Despite varied neuropathology, prominent frontal and temporal degeneration drive the clinical phenotypes. Three main proteins account for nearly all FTLDs. They are tau protein, the TAR DNA binding protein of 43 kDa (TDP-43), and the 'fused in sarcoma' protein (FUS). The majority of FTLDs are therefore FTLD-tau, FTLD-TDP, or FTLD-FUS. with any remaining FTLD pathology being relatively rare. Over 40% of FTLD cases have a family history of either or both dementia and movement disorder (Rohrer et al., 2009).

FTLD-tau is the most common of the group, with aggregation of p-tau in neurons and glia. The major subtypes of FTLD-tau are Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), globular glial tauopathy (GGT) and rare unclassifiable tauopathies. A frontotemporal dementia such as the clinically defined primary progressive aphasia, with its language-defined variants, may result from multiple pathologies, including FTLD-tau (29%) - primarily Pick's & FTLD-TDP (25%), AD (44%), or some combination of these or other pathologies (Mesulam et al., 2021).

Pick disease

Pick's disease (PiD) is a tauopathy, with a rare 3R tau aggregation, as opposed to the majority of tauopathies which are 4R. It usually presents clinically with deterioration of language, personality and judgment, including social disinhibition, and memory. While most cases are sporadic, a few familial cases have been linked to missense mutations in MAPT, also called frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).

Given the significant frontal and temporal lobe involvement, Pick's disease most often presents with behavioral and executive impairments, also known as behavioral variant FTD, but can present as primary progressive aphasia (Irwin et al., 2016). In one series, the mean age of onset was 57 +/-12 years, with mean disease duration of 9 years (Irwin et al., 2016). Loss of empathy was a common early feature and a large number of patients developed extrapyramidal features as the disease progressed. Axial rigidity, frequent falls, and disturbed eye movements all suggest supranuclear palsy, while asymmetric motor disturbance, alien limb syndrome, and ocular apraxia are associated with corticobasal syndrome.

FTDP-17 was used to describe cases of FTLD and Parkinsonism associated with mutations in MAPT (Hutton et al., 1998). Within the FTLD field, sporadic and genetic FTLD were initially considered separate entities, although cases are pathologically indistinguishable. However, another mutation on chromosome 17, on the progranulin gene, was also found to be associated with FTLD and cases of FTLD with MAPT mutations but without Parkinsonism were identified (Boeve and Hutton, 2008). There is phenotypic variability between

different FTDP-17 mutations and within the same mutation. For these reasons, it is recommended that FTDP-17 be considered a familial form of sporadic FTLD-tau- familial PiD (Forrest et al., 2018).

As in PiD, changes in personality and behavior are often early signs of FTDP-17, along with aphasia. Many affected individuals develop features of Parkinsonism, including tremors, rigidity, and bradykinesia, that is not generally responsive to levodopa. With disease progression, inability to walk, as well as difficulty with eye movements become prominent. Disease progression varies considerably from months to years.

Pick bodies, prominent neuronal inclusions in the form of ballooned neurons, are well delineated, round, neuronal cytoplasmic inclusions reactive to p-tau and 3R tau but negative for 4R tau (Kovacs et al., 2013). Such ballooned neurons are also seen in other tauopathies such as CBD and argyrophilic grain disease (AGD). Pick body-like inclusions in hippocampal dentate gyrus neurons in AD are different from Pick bodies of PiD, histologically and are both 3R and 4R positive (Kovacs et al., 2013). Glial lesions are less frequent than neuronal lesions in PiD, but Pick-body-like inclusions can be detected in oligodendrocytes in affected white matter. The neuroanatomical distribution of Pick bodies parallels brain atrophy. The circumscribed focal cortical atrophy ("lobar atrophy") is a striking neuropathological feature, particularly in the anterior frontal and temporal lobes, as well as in the medial and inferior temporal cortices, the so-called "knife-edge" atrophy. There is severe neuronal loss and gliosis and secondary axonal loss in the subjacent white matter. The striatum, subthalamic nucleus, and the substantia nigra are variably affected.

Corticobasal degeneration

Corticobasal degeneration is a sporadic 4R tauopathy with only a few MAPT mutations reported in rare familial cases. CBD symptoms typically begin in people from 50 to 70 years of age, and the average disease duration is six years. Patients present with cortical sensory deficits, alien limb phenomenon, highly asymmetrical Parkinsonism which progresses to dystonia and myoclonus. Additional features include apraxia and cognitive deficits. Tremor, when present, is a positional or action tremor and irregular. Dystonia is most often of the upper limb and less likely axial (Armstrong et al., 2013; Constantinides et al., 2019). Some patients PSP-like features such as postural instability and gaze palsy. PSP without CBD is estimated to be about ten times more common than PSP with CBD. CBD represents roughly 4–6% of patients with Parkinsonism.

Neuroimaging in CBD typically shows asymmetrical posterior parietal and frontal cortical atrophy, along with atrophy of the corpus callosum.

A key histopathological feature of CBD is the ballooned neuron which are swollen neocortical neurons containing p-tau. Importantly, CBD shares similarities with PSP in its prominent accumulation of 4R tau in both neurons and glial cells. Unlike the tufted astrocytes seen in PSP, tau-positive astrocytes in CBD appear as annular clusters of astrocytic cell processes, which have been named "astrocytic plaques" given their resemblance to neuritic plaques centered on Aß in AD (Chung et al., 2021). Oligodendroglial coiled bodies may also be found in CBD but are less prominent than those seen in PSP. Another prominent pathological feature of CBD is tau accumulation in neuronal processes as neuropil threads in affected gray and white matter of cortical and subcortical regions. Neuropil threads are also frequent in AD, where the term was originally used. The cerebral cortex and basal ganglia are preferentially affected in CBD, unlike in PSP where the basal ganglia, subthalamic nucleus, and midbrain are disproportionately impacted.

Progressive Supranuclear Palsy

PSP may be difficult to distinguish from Parkinson's disease (PD), especially in the early stages, because of overlapping clinical features. The diagnostic criteria for PSP include postural instability, akinesia, oculomotor dysfunction, and cognitive and lingual disorders. A common PSP variant, Parkinsonism predominant PSP is found in up to 35% of cases (Dale et al., 2020). PSP-P requires either akinetic-rigid predominantly axial and levodopa resistant Parkinsonism or Parkinsonism with tremor and/or asymmetric and/or levodopa responsive. Parkinson's disease with gait difficulty may be especially difficult to differentiate from PSP.

The initial symptoms in two-thirds of cases are loss of balance, lunging forward when mobilizing, and falls, beginning between age 60-70. Other common early symptoms are changes in personality common to FTD, general slowing of movement, and visual symptoms. Very rarely, cerebellar ataxia may be a presenting feature. The most common behavioral symptoms in patients with PSP include apathy, disinhibition, anxiety, and dysphoria. Other signs include facial muscle contracture, cervical dystonia, and vertical gaze paresis, with patients complaining of difficulty reading. However, this voluntary gaze paresis corrects with the oculocephalic

reflex. A wide stare accompanied by a furrowed forehead with a frown, termed the "procerus sign," is characteristic of PSP. Less than 1% of PSP patients have an affected family member.

Frequently misdiagnosed as Parkinson's, PSP is poorly responsive to levodopa and rarely presents with a rest tremor. Eye movement abnormalities, pathognomonic in PSP are uncommon in PD. In addition to frequent falls early in the course of the disease, PSP patients also present with an arched or a straight back rather than the stooped posture of PD. Supportive care is the only management currently available for PSP.

PSP is characterized by neuronal and glial tau pathology, neuronal loss, and fibrillary astrogliosis, with the most severe neuronal loss found in the globus pallidus, subthalamic nucleus, and substantia nigra. Globose NFT or pretangles are frequent in these affected brain regions(Chung et al., 2021). As with other tauopathies, PSP pathology may coexist with that of CBD, AD and Lewy bodies.

Globular glial tauopathy

Globular glial tauopathy (GGT) is a rare non-familial 4R tauopathy, with a few cases linked to MAPT mutations. The clinical spectrum of GGT spans FTLD, motor neuron disease (MND) and both, leading to three GGT subtypes. In each GGT subtype (Ahmed et al., 2013, 2011), FTD-like symptoms reflect tau pathology affecting frontal and temporal cortices, while MND-like symptoms correspond to involvement of motor cortex and corticospinal tract degeneration. Type I, with pathology in the frontal lobe, can present as FTD or PiD, with predominantly FTD clinical features. Type II GGT with pathology in the motor cortex and corticospinal tract, presents with pyramidal and extrapyramidal features, and is often misdiagnosed as PSP, CBS, motor neuron disease or primary lateral sclerosis. Type III, with involvement of the frontotemporal lobe as well as motor cortex and corticospinal tract, presents with dementia and frontal lobe features, motor neuron disease and is often misdiagnosed as PSP, CBS, or motor neuron disease.

The major histopathological hallmarks of GGT are 4R tau enriched, globular, tau-positive globular astroglial inclusions (GAIs) and oligodendrocytes and globular oligodendroglial inclusions (GOIs). There are significant differences in seeding potency of GGT brain lysates in cell-based reporter assays compared to brain

lysates of other tauopathies such as PSP, CBD, and AD, supporting the concept that GGT is a distinct tauopathy (Chung et al., 2019).

Anti-IGLON5 -related tauopathy

This recently described tauopathy is characterized by a unique rapid eye movement (REM) parasomnia with sleep apnea and stridor, accompanied by bulbar dysfunction and specific association with antibodies against the neuronal cell-adhesion protein IgLON5 (Werner et al., 2021). Patients present at a median age of 70 with recurrent respiratory distress and progressive neurogenic dysphagia. They may be misdiagnosed as a motor neuron disease, with time from symptom onset to diagnosis of 2 years. In one series, all patients had dysarthria, muscle spasticity, hyperreflexia, atrophy and limb weakness and occasional tongue and extremity fasciculations. Treatment with systemic corticosteroids may be of benefit.

The pathology is restricted to neurons and predominantly involves the hypothalamus and tegmentum of the brainstem with the neuronal accumulation of hyperphosphorylated tau composed of both three-repeat (3R) and four-repeat (4R) tau isoforms (Ganguly and Jog, 2020; Gelpi et al., 2016).

Argyrophilic Grain Disease

Argyrophilic grain disease (AGD) is widely prevalent and just as widely unrecognized (Ferrer et al., 2008). The term argyrophilic grains was coined by Braak and Braak to describe numerous spindle-shaped 4R tau-positive profiles scattered in the neuropils of demented patients without AD tau pathology (Braak and Braak, 1998). AGD is virtually unknown in clinical neurology because most cases are asymptomatic although some cases present with a dementia that is indistinguishable from AD. It is the second most common tauopathy after AD, with an incidence ranging from 9% in 65-year-olds to 31 % in centenarians.

In clinical cases, personality changes and psychiatric symptoms may be the presenting features and cognitive impairment may or may not be present. AGD may be an etiology of late-life psychosis. Interestingly, semantic memory impairment is not seen in AGD.

To make matters complicated, AGD pathology frequently is seen with AD and other tauopathies, as well as in non-tau neurodegenerative disorders such as Lewy body disease. In 545 serial autopsy cases from a

general geriatric hospital, 18% of patients with both mild cognitive impairment and dementia had neuropathology consistent with AGD. AGD was found in a third of the brains of a series of cognitively normal subjects (Knopman et al., 2003). In PSP, the frequency of AGD ranges from 19-80% (Rodriguez and Grinberg, 2015). In CBD, AGD pathology is found in 41-100% of cases (Ferrer et al., 2008; Yokota et al., 2018). It is not always easy to distinguish argyrophilic grains from cross sections of dystrophic neurites of AD pathology, and when appropriate stains are used, AGD copathology increases to over a quarter of all AD cases (Yokota et al., 2018).

AGD progresses from the anterior entorhinal cortex, amygdala, and lateral hypothalamus to the entire entorhinal cortex, anterior CA1, eventually involving the neocortex and brain stem, as is characteristic of tau propagation (Saito et al., 2004).

Primary age-related tauopathy

Primary age-related tauopathy (PART) was previously considered normal aging or neurofibrillary tangle predominant senile dementia (Crary et al., 2014). Cognitively normal persons may exhibit pathologically definite PART. Cognitive impairment in PART is more often seen in those over 80 years of age with a family history of cognitive disorders. Even patients with severe PART typically exhibit mild cognitive loss and on occasion dementia but most patients with PART are asymptomatic.

There are AD-like NFTs composed of PHFs, and positive for 3R and 4R tau, which is neuronal, as in AD, and unlike other tauopathies (Ferrer et al., 2020). However, unlike AD, PART is not associated with amyloid copathology or the APOE4 allele (Crary et al., 2014). PART can overlap with some types of FTLD-tau. “Definite PART” reveals frequent NFTs in the limbic system, including CA2 region of the hippocampus, amygdala, and medial temporal lobe. “Possible PART” refers to patients with similar NFT pathology, with concomitant mild amyloid co-pathology.

Aging-related tau astrogliopathy

Aging-related tau astrogliopathy (ARTAG) may present clinically with focal symptoms like aphasia when circumscribed to a small region. ARTAG is generally seen in persons 60 years and older and is rarely an isolated finding. A common co-pathology, ARTAG is detected in more than 65 % of primary tauopathies. In cases with widespread pathology, dementia with or without Parkinsonism, might be the clinical presentation.

While the etiology and clinical significance of ARTAG are poorly understood, studies have shown that ARTAG is associated with significantly elevated levels of another astrocytic protein, aquaporin-4, and the major water channel in the brain. This suggests a role for blood-brain barrier dysfunction in the pathogenesis of ARTAG (Kovacs et al., 2018).

ARTAG is defined by the presence of 4R tau-positive thorn-shaped astrocytes in subpial, perivascular and subependymal regions mostly in aged individuals, without neuronal involvement (Kovacs et al., 2016). A subtype of ARTAG presents with tau-positive granular/fuzzy astrocytes in the gray matter, especially in the amygdala. While astrocytic tau lesions are characteristic of other primary tauopathies such as PSP, CBD, and GGT, they are also observed in brains of neurologically normal elders (Kovacs, 2020).

Tauopathies Due to Environmental Exposures

Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a sporadic tauopathy associated with repetitive traumatic brain injuries and related sub-concussions and concussions. Contact sport players and military personnel are most at risk, particularly American football players. In a population-based autopsy cohort of those with a history of playing contact sports, both athletes and nonathletes, 6% had CTE. In autopsies of gridiron football players, 99% of NFL players, 88% of college football players, and 64% of semi-professional players had evidence of CTE (Bieniek et al., 2020).

Symptoms generally appear at least 8-10 years after exposure to repeated brain injury although a single moderate injury can lead to CTE (Smith et al., 2019). Patients present with significant headaches, progressive behavioral and mood problems, attentional and memory deficits progressing to a frank dementia. Some patients

develop dysarthria and muscle atrophy, with motor neuron type features. Parkinsonism and tremors may present in some patients along with gait imbalance. Some patients with CTE have chronic traumatic encephalomyelopathy with symptoms of motor neuron disease, muscle weakness, and ataxia (McKee et al., 2010). Prevention with helmets and avoidance of repeated concussions is key.

The pathology of CTE needs is to be distinguished from that of ARTAG, as both are found in the depths of the cortical sulci. CTE pathology is characterized by perivascular neuronal and glial tau lesions, while ARTAG spares neurons. CTE pathology is in an unpredictable distribution, while there is a characteristic distribution and progression in ARTAG (Chung et al., 2021). At the advanced disease stage, tau pathology in CTE is found in most cortical regions, including the medial temporal lobes. Progressive involvement of basal ganglia and brainstem is accompanied by pronounced brain atrophy. Additionally, diffuse Aß plaques can be detected in a subset of CTE, especially in older individuals.

The conformation of tau filaments in CTE is distinct from that of AD, despite the shared 3R and 4R tau pathology. A unique hydrophobic cavity in the CTE tau core suggests that as yet unidentified factors contribute to CTE specific tau aggregation.

Geographically isolated PSP-like tauopathies

Guam Parkinsonism-dementia complex

Guam Parkinsonism-dementia complex (PDC) is a geographically isolated tauopathy found in the Mariana Islands, the Ki peninsula of Japan and the coastal plain of West New Guinea (Steele, 2005). The Chamorro population of Guam call it Lytico-bodig.

Patients manifest Parkinsonism, with tremor, rigidity and bradykinesia as well as muscle atrophy, spasticity, maxillofacial paralysis, dysarthria, and dysphagia. A progressive dementia with restlessness, agitation, and pseudobulbar symptoms occur at the end stages with eventual paralysis of the respiratory musculature. Hirano dubbed it ALS-PDC because of the motor neuron and Parkinson's disease features (Hirano, 1992).

Consumption by the Chamorro of bats feeding on Federico nuts (Cycas micronesica) with B-methylamino-L-alanine, a neurotoxin or consumption of cycad seeds is thought to trigger the condition (Steele, 2005). Declining consumption of bats has led to reduction in incidence of the disease. The age at onset is also increasing as the result.

Neuropathological features of Guam PDC include cortical atrophy and depigmentation in the substantia nigra and locus ceruleus. As with AD, Guam PDC exhibits 3R- and 4R-positive NFT pathology extensively distributed in the neocortex, hippocampus, and brainstem, but mostly in the absence of senile plaques. Neuropil threads are seen. Both gray and white matter are affected by tau pathology, and unlike AD, glial tau inclusions are often detected in Guam PDC in astrocytes and oligodendrocytes (Winton et al., 2006).

Guadeloupean Parkinsonism

This tauopathy was seen among residents of the Guadeloupe islands in the French West Indies in the late 1990's. Clinically, these individuals displayed an atypical Parkinson syndrome with PSP-like features such as postural instability and vertical gaze impairment. Consumption of herbal teas and fruits containing alkaloid toxins that are potent inhibitors of mitochondria was associated with the condition (Caparros-Lefebvre et al., 2002). Histopathological analysis revealed pretangles, NFTs, and threads composed of hyperphosphylated tau in multiple brain regions including the midbrain, the striatum, and the cortex.

Northern France Tauopathy

Exposure to soil highly contaminated with arsenic and chromate from chemical plants may have contributed to an approximately 12-fold more than expected spike of PSP-like tauopathy in France from 2007-2014 (Caparros-Lefebvre et al., 2015). Patients often showed gait and gaze abnormalities.

Other conditions with tau aggregates

Tau has also been described in Gerstmann– Sträussler– Scheinker disease, myotonic dystrophy, post-encephalitic Parkinsonism, prion protein cerebral amyloid angiopathy, SLC9A6 - related mental retardation, subacute sclerosing panencephalitis and Down’s syndrome (Goedert, 2011).

Secondary tauopathies

Alzheimer Disease

Alzheimer's disease (AD), the most common form of dementia, is a secondary tauopathy requiring both Aß amyloid deposition and tau aggregation for diagnosis. Most cases are sporadic and present in their 60s, 70s, and 80s, although rare familial cases, which constitute less than 2%, become symptomatic in their twenties (Devi et al., 2000). While memory impairment is the most common complaint, impairment of many other cognitive domains, including language and praxis may be an early feature. The prodromal phase of mild cognitive impairment may last many years. Illness trajectory and treatment response are influenced by coexisting brain pathology, systemic co-morbidities, and sociodemographic variables including activity and educational level.

The condition may best be considered a syndromic disorder rather than a monolithic disease, with varying presentations and prognosis based on the brain regions affected, and the individual's brain and cognitive reserve (Devi, 2018). Neuropathological subtypes include limbic predominant, hippocampal sparing, and diffuse Alzheimer's, based on the pattern of NFT deposition (Ferreira et al., 2020; Murray et al., 2011). The hippocampal sparing subtype of AD is most often associated with younger age, earlier motor symptoms, and a more aggressive progression (Ferreira et al., 2020). Based on neurocognitive profiles, up to 8 cognitive clusters may be discerned, with distinct demographics, symptoms, and progression (Scheltens et al., 2016).

Because of the existence of tau and other neurodegenerative copathology, and the tremendous symptom overlap between these diseases and normal aging, clinical diagnosis without biomarker confirmation is challenging. Sensitivity for a clinical diagnosis of AD in memory disorder centers ranged from 71 to 87% and specificity ranged from 44 to 81% (Beach et al., 2012). In an autopsy series of 184 persons with neuropathological AD, about a third had AD-only pathology, 50% had additional TDP-43 pathology, 22% had additional α-synuclein pathology, and 18% had additional combined α-synuclein and TDP-43 pathology. To

further complicate matters, within each of these pathologically defined groups, between 30% and 50% of individuals had at least one infarct (Karanth et al., 2020).

The greatest risk factors for sporadic Alzheimer's disease are older age, female gender, and the *APOE* ε4 allele. The ε4 allele increases the risk for dementia by 3–4 times when compared with ε3 carriers. Cardiovascular risk factors and an unhealthy lifestyle are associated with an increased risk. Rare protein-damaging variants in the *SORL1*, 46 *ABCA7*, 47 and *TREM2* genes also increased risk, as intact protein products of these genes are essential for brain health (Scheltens et al., 2021). Mutations in the presenilin (PSEN)1 gene on chromosome 14 and the PSEN2 gene on chromosome 1 are the most common causes of familial AD.

Clinical and biomarker diagnosis

Formalizing a diagnostic approach to Alzheimer's disease began with criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's and Related Disorders Association in 1984 which excluded other possible causes of dementia (McKhann et al., 1984). The International Working Group advocated, in 2010, for a diagnosis that incorporated biomarkers into the diagnostic framework (Dubois et al., 2010). In 2018, a purely biomarker amyloid, tau, and neurodegeneration (ATN) method of diagnosis was recommended (Jack et al., 2018). A combined clinical biomarker approach seems to be the most valid, as a solely biomarker-based approach has significant issues (Dubois et al., 2021).

Low cerebrospinal fluid (CSF) levels of Aβ in conjunction with high phosphorylated tau levels are consistent with a diagnosis of AD. Even in cognitively normal persons, 80% of those with abnormal CSF biomarkers progress to MCI in 6 years, while 90% of those with cognitive impairment develop dementia within a decade (Buchhave, 2012). Positron emission tomography (PET) to detect amyloid plaque and tau biomarkers are non-invasive, albeit expensive, imaging approaches. Cognitively normal individuals as well as others with MCI and abnormal Aβ PET imaging are at increased risk for dementia (Jack et al., 2019).

New biomarkers being investigated include neurogranin increases early in the disease and is specific for Alzheimer's disease. Levels of neurofilament light are increased in blood proportionate to CSF levels, making

this an easy access biomarker. CSF biomarkers in AD differ from the FTLDs, helping with diagnostic clarification (Mattsson-Carlgren et al., 2022; Schöll et al., 2019).

Pathology

AD can be conceived of as a synaptic dysfunction disorder leading to failure of cortical circuitry (Knopman et al., 2021). Synaptic pathophysiology unifies genetic, neuropathologic and clinical manifestations of AD and synaptic loss strongly correlates with cognition loss.

Aβ peptides, the additional protein found in aggregates in AD, are formed in the extracellular space by cleavage of the transmembrane amyloid precursor protein. Amyloidogenic, aggregation-prone, longer-chain Aβ oligomers formed by the action of β- and γ- secretases are components of amyloid plaques, while shorter, soluble Aβ peptides formed by α-secretase are excreted. Aβ amyloid plaques are surrounded by decreased synaptic content for ~50 μm, with presynaptic and postsynaptic marker loss (Spires-Jones and Hyman, 2014). Given the quantity of amyloid plaques in patients with AD, this translates to immense synaptic dysfunction and loss.

Aβ plaques may serve a protective function, helping to sequester and neutralize amyloidogenic Aβ oligomer neurotoxicity. The theory that longer-chain Aβ oligomers, rather than insoluble Aβ plaques, cause synaptic dysfunction is supported by the 'Osaka' mutation, found in a familial form of AD. This mutation accelerates Aβ oligomerization but does not form amyloid fibrils or plaques, with rapid onset of dementia with characteristic Aβ and tau levels in CSF without the presence of plaques (Tomiyama and Shimada, 2020). Additionally, this is the only known early onset AD mutation with a recessive inheritance.

Although Aβ begins to accumulate10–20 years prior to cognitive symptoms, tau accumulates in the temporal and parietal isocortex at a time much more proximate to cognitive impairment and continues to accumulate parallel with disease progression (Knopman et al., 2021). Tau is therefore more helpful with plotting disease progression. Additional alterations in microglia, and astroglia drive disease progression before cognitive impairment is observed. Neuro-inflammation, alterations in vasculature, and dysfunction of the glymphatic system, act in tandem or upstream to accumulating amyloid β.

As first proposed by Braak and Braak, NFT pathology first develops in the trans-entorhinal cortex and subsequently appears in the limbic system, including the hippocampus and amygdala, then isocortical regions, finally involving the primary cortices at the advanced and end stages (Braak and Braak, 1995). Tau lesions in AD include NFTs and neuropil threads composed of PHFs and straight filaments (SFs) that are immunoreactive for both 3R and 4R tau. Tau-positive glial lesions are not a feature of AD unless there is a comorbidity with other tauopathies such as ARTAG or AGD, which occurs often. On the other hand, reactive astrocytes and activated microglia are frequently detected in affected brain regions in AD.

Treatment

This section details treatment of tauopathies and cognitive impairment in general and of Alzheimer's disease specifically. Prevention is important both for environmentally associated tauopathies and for AD. The SPRINT-MIND trial found intensive blood pressure control with a systolic blood pressure <120 mm Hg is more effective in reducing the risk of cognitive impairment than standard blood pressure control (Williamson et al., 2019). The Finnish FINGER study, a long-term, randomized controlled trial found that a multidomain lifestyle-based intervention can reduce the risk of cognitive impairment among at risk persons, even in persons with genetic risk factors for AD (Kivipelto et al., 2018). FINGER interventions were multipronged, with healthy balanced nutrition, physical exercise, cognitive training and social activities, and vascular and metabolic risk management.

Symptomatic treatment for the tauopathies include the use of levodopa to help with parkinsonian features, although they have generally not been helpful. Antidepressants including the selective serotonin reuptake inhibitors such as citalopram and atypical antipsychotics such quetiapine are helpful with mood and behavioral disturbances, although atypical antipsychotics increase risk of all-cause mortality. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine may help slow cognitive decline and reduce mortality for as long as six years in patients with AD and other dementias (Zuin et al., 2022). Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist slows cognitive decline in both mild and moderate AD and may have neuroprotective properties (Lipton, 2007; Wu et al., 2009).

Aside from symptomatic treatments, disease modifying agents have focused on anti-amyloid (oligomer or plaque), anti-tau antibody, anti-inflammatory, and other treatments. Neuroinflammation is recognized as a major component of the pathology of Alzheimer's disease, contributing to disease progression and neurodegeneration. Extracellular amyloid plaques may activate the surrounding microglial immune response in a sustained feedforward loop that exacerbates pathology. Microglia modulate inflammation along with the nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing receptor 3 (NLRP3) inflammasome. Activity of the NLRP3 inflammasome promotes tau pathology, with mice that are NLRP3 deficient showing less tau pathology and less hippocampal degeneration (Stancu, et al., 2022). Oligomannate, derived from seaweed with anti-inflammatory properties, was approved in China and associated with cognitive improvement (Wang et al., 2019).

Tau immunotherapy, where humanized tau antibodies have reached clinical trials for AD, PSP, and PPA have been of promise, although the tau antibody, semorinemab, recently failed to stem tau deposition despite extremely high doses (Teng et al., 2022). As tau is primarily intracellular, antibodies that do not reach cytosolic tau may not be effective. Additionally, pathogenic tau species differ between patients (Dujardin et al., 2020).

Anti-amyloid treatments for AD include aducanumab, which has been conditionally approved by the United States Food and Drug Administration (FDA), lecanemab, which is currently being evaluated for approval by the FDA, and ALZ-801 | tramiprosate, currently in a phase 3 trial (Table 2). A shared feature of these drugs is their engagement of neurotoxic soluble oligomers. While aducanumab targets oligomers, its major focus is insoluble amyloid plaques. Lecanemab preferentially targets soluble protofibrils (large oligomers) over plaques. ALZ-801 | tramiprosate blocks the formation of oligomers without any effect on plaque. All three also reduce downstream tau (Tolar et al., 2020). Additionally, both aducanumab and lecanemab show amyloid related imaging abnormalities (ARIA) as side-effects, with brain edema and microhemorrhages related to plaque dissolution, and both are parenterally administered. A slower dose titration appears to significantly lessen aducanumab related ARIA. It is of note, however, that several anti-amyloid therapies have failed, confounding the amyloid hypothesis for pathogenesis in AD and pointing to tau as the culprit (Hernandez et al., 2018).

Table 2

Selected anti-amyloid agents for AD

Drug	Route/ frequency	Half-life	Brain Penetration	Amyloid Oligomer selectivity	Amyloid PET % reduction	CSF p-tau % benefit v placebo	ARIA	Cognition ADAS-Cog % benefit versus placebo	Function CDR-SB % benefit v placebo
Aducanumab	Intravenously monthly	21 day	<1.5%	+/-	80%	15%	35-42%	27%	27%
Lecanemab	Intravenously every 2 weeks	5 day	~ 0.5%	+/-	90%	13%	10%	47-80%	26-60%
ALZ-810 | Tramiprosate	Orally twice daily	36 hour	~ 40%	+++	No effect	Not evaluated	0%	125%	81%

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale's cognitive (ADAS-Cog) subscale; ARIA, amyloid-related imaging abnormalities; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; PET, positron emission tomography.

Precision medicine is particularly relevant for treating tauopathies, given not only the tremendous variability in clinicopathology, but also the inherent inter-individual variability of the human brain (Devi and Scheltens, 2018). Over 83% of ongoing trials for AD are targeted toward modifying disease, either via anti-amyloid or anti-tau pathways, or through other mechanisms, using diverse agents such as amlodipine, metformin, and hydralazine, while the remainder focus on ameliorating cognitive and neuropsychiatric symptoms (Cummings et al., 2022).

Conclusions

Aberrant neuronal and glial tau aggregation is a shared feature of tauopathies. The regional, morphologic, and cell-type variability with the resultant vast heterogeneity in clinical illnesses, underscores the importance of distinct disease-specific pathomechanisms in tauopathies. Understanding the mechanisms of tau aggregation and their role in neurotoxicity based on type of tau aggregate and cell-type predilection is important. It is still unclear what molecular steps lead from conformational changes in tau to neuronal cell death. Known genetic mutations and environmental causes must be integrated with the dysregulated molecular pathways seen in sporadic cases. One crucial question is understanding which inclusions are neurotoxic and

which ones may be neutral or even protective to the central nervous system. Various therapeutic strategies are being developed to target tau from anti-aggregation agents to immunotherapy. Given the heterogeneity of the disorders, it is unlikely that an effective therapeutic approach for one type of tauopathy, or even one subtype, or even in one individual, may be beneficial for another.

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