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Astrocytes in tauopathies

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Abstract

Tauopathies are a group of neurodegenerative diseases characterised by the progressive accumulation across the brain of hyperphosphorylated aggregates of the microtubule-associated protein tau that vary in isoform composition, structural conformation and localisation. Tau aggregates are most commonly deposited within neurons but can show differential association with astrocytes, depending on the disease. Astrocytes, the most abundant neural cells in the brain, play a major role in synapse and neuronal function, and are a key component of the glymphatic system and blood brain barrier. However, their contribution to tauopathy progression is not fully understood. Here we present a brief overview of the association of tau with astrocytes in tauopathies. We discuss findings that support a role for astrocytes in the uptake and spread of pathological tau, and we describe how alterations to astrocyte phenotype in tauopathies may cause functional alterations that impedes their ability to support neurons and/or cause neurotoxicity. The research reviewed here further highlights the importance of considering non-neuronal cells in neurodegeneration and suggests that astrocyte-directed targets that may have utility for therapeutic intervention in tauopathies.

Contribution to the field: Several neurodegenerative diseases, including Alzheimer's disease are characterised by the presence of abnormal tau deposits in affected brain regions, that is closely associated with synapse loss and neurodegeneration. Astrocytes, the most abundant neural cell type are an intrinsic component of synapses and regulate neuronal circuits. Recent evidence has highlighted an important contribution of astrocytes to the prion-like propagation of abnormal tau in Alzheimer's disease and related tauopathies. We discuss the evidence linking astrocytes with tauopathies, including their newly described roles in tau uptake/spread, highlighting the importance of continued work in this area.

1 Introduction

Tauopathies are a heterogeneous group of neurodegenerative diseases in which the deposition of hyperphosphorylated tau aggregates in affected brain regions accompanies synapse and neuron loss (Guo et al., 2016). Primary tauopathies exhibit tau aggregates as the predominant pathological hallmark and include a diverse family of frontal-temporal lobar dementia (FTLD) subtypes referred to as FTLD-tau, and includes progressive supranuclear palsy (PSP) and Pick's disease (PiD).

Alzheimer's disease (AD) is considered a secondary tauopathy owing to the presence of extracellular amyloid-beta (Aß) plaques, and is the most common cause of dementia (Prince et al., 2014).

Tau proteins undergo several post-translational and other modifications in disease (Guo et al., 2016). Modified forms of tau spreads from the original site of deposition to anatomically connected regions by a "prion-like" mechanism, whereby tau proteopathic seeds passively recruit tau monomers (Jucker and Walker, 2018). The mechanisms underlying tau release, uptake and spread are not fully understood. It has long been acknowledged that in some tauopathies astrocytes accumulate tau leading to characteristic disease neuropathology. Accumulating evidence now suggests that astrocytes may actively participate in tau spread and/or clearance mechanisms by actively internalising tau. This review summarises the association of tau with astrocytes in tauopathies, and discusses the evidence implicating astrocytes in tau spread, as well as the impact of tauopathy brain environments on physiological astrocytic functions.

2 Tau protein

Human tau is encoded by the *MAPT* gene on chromosome 17 which comprises 16 exons. Exons 2, 3 and 10 undergo alternative splicing to produce the six main tau isoforms present in the adult human central nervous system (CNS) (Andreadis, 2005). Alternative splicing of exon 10 gives rise to tau isoforms containing either three or four microtubule binding repeats (referred to as 3R or 4R tau) in the C-terminal region, and alternative splicing of exons 2 and 3 produces tau proteins with zero, one or two inserts in the N-terminal tail (0N, 1N or 2N tau, respectively). A conserved proline-rich domain is found between these two spliced regions and is known to be important for tau interactions with other proteins, including actin (He et al., 2009). Tau isoforms are developmentally regulated; the shortest 0N3R isoform is expressed in the fetal brain whereas in the adult human brain 3R and 4R isoforms are equally represented (Goedert and Jakes, 1990). Tau has a number of key functions, the most recognised of which is stabilising microtubules in the axons of neurons, however tau roles in other important physiological functions such as axonal transport, DNA protection, cell signalling at the membrane, and synaptic vesicle release, have been described (Wang and Mandelkow, 2016; Guo et al., 2017). Tau is primarily expressed in neurons (Binder, 1985), but is known to be expressed to a lesser extent in glial cells (Zhang et al., 2014; Darmanis et al., 2015; Seiberlich et al., 2015; McKenzie et al., 2018).

Monomeric tau is water soluble and resists aggregation (Wang and Mandelkow, 2016). In tauopathies, tau undergoes extensive post-translational and other modifications including, but not limited to, phosphorylation, acetylation, nitration, SUMOylation, glycosylation, ubiquitination, cleavage and aggregation (Guo et al., 2017). The best studied of these is phosphorylation. There are 85 potential phosphorylation sites in 2N4R tau (Hanger et al., 2009) and increased phosphorylation of tau, alongside other tau modifications, can reduce tau affinity for microtubules, increase cytoplasmic tau concentrations and promote tau oligomerisation and aggregation (Guo et al., 2017). Differential extents of tau modifications lead to the accumulation of heterogeneous pools of modified tau between, and within, different tauopathies. Recently, Dujardin et al. (2020) found variations in relative abundance of soluble, oligomeric and seed-competent species of hyperphosphorylated tau in tauopathy brain. Specific post-translational modifications were found to influence tau seeding capacity, and tau seeding potential strongly correlated with the rate of clinical symptoms/disease progression.

The isoform composition of tau aggregates, as well as the structure of tau filaments, also differs between tauopathies. In AD, both paired helical and straight filaments contain identical protofilament

cores comprising residues 306-378 that define the aggregatory seed/core (Fitzpatrick et al., 2017). This structure differs from the folds of tau filaments observed in Pick's disease (Falcon et al., 2018) and tau filaments of chronic traumatic encephalopathy (CTE) have a unique hydrophobic core (Falcon et al., 2019). A novel fold in corticobasal degeneration (CBD) tau has now also been discovered (Zhang et al., 2020). These features may be important for the tau lesions that arise in different tauopathies (Table 1).

3 Astrocytes in health and disease

Astrocytes are organised into distinct domains, and each astrocyte can connect with thousands of neurons, allowing them to coordinate synaptic activity in the CNS (Parpura et al., 1994; Oberheim et al., 2006). Astrocytes were long considered as supporting cells in the brain, providing metabolic and nutritional support for neurons. However, astrocytes are critical for neuronal function due to their ability to sense changes in neuronal activity through their complement of cell surface receptors, and to modulate neuronal activity by releasing gliotransmitters and gliomodulators, as well as controlling the availability of glutamate, GABA and energy substrates (Parpura et al., 1994; Volterra and Meldolesi, 2005; Choi et al., 2014). Hence, astrocytes are now known to be actively involved in synaptic transmission (Santello et al., 2019), neural circuit maintenance (Mederos et al., 2018) and long-term potentiation (Lushnikova et al., 2009). In addition, astrocytic end-feet are a structural component of the blood-brain barrier (BBB), and together with endothelial cells and pericytes have a central role in the regulation of blood flow (Sofroniew and Vinters, 2010). Furthermore, astrocyte end-feet are crucial for the glymphatic system of the brain, a perivascular network that allows for exchange of interstitial and cerebrospinal fluid (CSF), providing a route for clearance of molecules and proteins including Aβ (Iliff et al., 2012; Simon et al., 2018).

In the neurodegenerative brain, astrocytes undergo pathological changes in responses to changes in the local brain environment that precede neuronal loss (Kersaitis et al., 2004). These morphologically and functionally modified astrocytes are often termed 'reactive'. Reactive astrocytes show considerable heterogeneity related to their localisation in the brain and the severity and length of injury/insult to their local environment (Zamanian et al., 2012). Reactive astrocytes are traditionally characterised by increased levels of glial fibrillary acidic protein (GFAP), which allows cytoskeletal and morphological arrangements as astrocytes alter their function (Kamphuis et al., 2015; Acosta et al., 2017). The accumulation of GFAP-immunopositive astrocytes is common in neurodegenerative diseases. For example, reactive astrocytes are often found surrounding plaques in AD (Bouvier et al., 2016; Osborn et al., 2016). Indeed, levels of GFAP-reactive astrocytes are closely associated with dementia in AD (Perez-Nievas et al., 2013). While increased GFAP is also found in aged brain (Wruck and Adjaye, 2020), new evidence suggests that there are subgroups of astrocytes, with varying levels of GFAP expression, that distinguish aging from AD, at least in mice (Habib et al., 2020). Alterations in GFAP expression have also been noted in primary tauopathies including PSP, PiD and corticobasal degeneration (CBD) (Ferrer et al., 2014).

Functional changes in reactive astrocytes are well-documented and include impaired gliotransmitter release (Piacentini et al., 2017), alterations in calcium signalling (Shigetomi et al., 2019), deficient ability to regulate glutamate levels at neuronal synapses and aberrant GABA release (Acosta et al., 2017). In addition, astrocytes are now recognised to contribute to neuroinflammatory responses that accelerate the progression of neurodegenerative diseases (Phillips et al., 2014; Bouvier et al., 2016; Bright et al., 2019). For example, reactive astrocytes increase their production and release of pro-inflammatory cytokines, complement components, and reactive oxygen species, alongside downregulating anti-inflammatory and repair proteins to induce neurotoxicity in diseased

environments (Lian et al., 2015; Bouvier et al., 2016; Leyns and Holtzman, 2017; Sadick and Liddelow, 2019). Recent seminal findings proposed that astrocytes respond to their local environment by adopting "A1-neurotoxic" or "A2-neuroprotective" phenotypes (Liddelow et al., 2017). Secretion of Il-1α, TNFα, and C1q by microglia in response to damage, induces astrocytes to upregulate their expression of a specific cluster of "A1" genes, lose their trophic and synaptic support for neurons, and induce neuron death (Liddelow et al., 2017). Markers of A1 astrocytes are upregulated in AD and other neurodegenerative diseases (Liddelow et al., 2017), strongly implicating microglia-astrocyte communications in neurodegeneration. However, it is likely that there is a spectrum of reactive astrocyte states in different brain regions, throughout aging and disease progression (Boisvert et al., 2018; Habib et al., 2020), similar to dynamic microglial responses in disease (Vainchtein and Molofsky, 2020).

4 The association of astrocytes with tauopathy

Tau aggregates accumulate in both neurons and astrocytes in different tauopathies. In AD, tau aggregates containing both 3R and 4R tau deposit as intraneuronal neurofibrillary tangles and there is scant evidence of astrocytic tau inclusions (Garwood et al., 2017). In contrast, astrocytic tau pathology is the defining feature of several FTLD-tau subtypes (Table 1). In PSP, a neuropathological diagnosis criterion is 'tufted' astrocytes that show 4R tau aggregates in their proximal processes (Cairns et al., 2007; Kovacs and Budka, 2010). CBD has extensive clinical overlap with PSP. In CBD, astrocytic plaques containing 4R tau deposits that mark distal and end processes are an exclusive feature in most (Forrest et al., 2019), but not all (Ling et al., 2020) cases. Thread-like tau-positive astrocytic processes are also common in CBD (Dickson et al., 2011; Ling et al., 2016). Argyrophilic grain disease (AGD) is a rare tauopathy that is characterised by 4R tau-immunopositive astrocytes, described as thorn-shaped and fuzzy/bush-like, in the medial temporal lobe (Botez et al., 1999; Saito et al., 2004; Forrest et al., 2019). In contrast, PiD is typically characterised by neuronal 3R tau inclusions, predominantly in granular neurons in the hippocampus, frontal and temporal cortices (Dickson, 2001; Josephs et al., 2011). 'Ramified' astrocytes immunopositive for tau have also been reported in PiD, but they are not considered a major pathological hallmark of the disease (Dickson et al., 2011; Ferrer et al., 2014). Several rarer tauopathy subtypes that show 4R tau-immunopositive globular inclusions, predominantly in oligodendrocytes, and more rarely in the cytoplasm and proximal processes of astrocytes, are collectively termed globular glial tauopathy (GGT) (Ahmed et al., 2013).

A spectrum of FTLD-tau subtypes that accumulate both 3R and 3R tau in neurofibrillary tangles (NFTs) typically occurring in cognitively normal aged individuals is referred as primary age-related tauopathy (PART) (Crary et al., 2014; Jellinger et al., 2015). Depending on the co-occurrence of Aß pathology, PART can be histologically classified as "definite PART" in the absence of Aß deposits, or "possible PART" when a limited number of Aß deposits are present (Crary et al., 2014). Although the neuropathological characteristics of PART can overlap with other tauopathies, particularly AD, PART shows a lower threshold of amyloid load, and appears to have a more limited impact on cognition (Crary et al., 2014). Tau pathology in PART is predominantly neuronal and found in the CA2 hippocampal subfield, with little evidence of astrocytic tau deposits (Crary et al., 2014; Jellinger, 2018). In contrast, age-related tau astrogliopathy (ARTAG) describes a spectrum of abnormal tau pathology, predominantly in the aged brain, that is characterised by thorn-shaped and granular or fuzzy astrocytes containing phosphorylated tau (Kovacs et al., 2016; Kovacs, 2018). ARTAG can present alongside more typical tau pathology in tauopathies such as CBD (Kovacs et al., 2018, 2020), but is not always linked with dementia (Lace et al., 2012). In a recent detailed review, Kovacs et al. (2020) describe two distinct distribution patterns of ARTAG. They describe

ARTAG as a consequence of repeated mechanical damage (related to CTE), or chronic damage such as blood-brain barrier dysfunction. Furthermore, they propose that the location and type (white versus grey matter) of ARTAG pathology may result in decompensation of cognitive functions, the rate of which may be influenced by co-existing pathologies (Kovacs, 2020). It is important to note that the presence of astrocytic tau accumulations in the absence of dementia may suggest that tau-containing astrocytes are not damaging in tau-associated neurodegeneration, or at least in ARTAG, and may internalise tau aggregates as a means of clearing damaging protein species.

Finally, chronic traumatic encephalopathy (CTE) is caused by mild repetitive head injuries. 3R and 4R tau-positive aggregates are common in CTE, however the tau aggregates that accumulate in astrocytes are predominantly 4R and localize in astrocytes near small vessels in the cerebral sulci of the frontal and temporal cortices (McKee et al., 2013, 2015; Stein et al., 2014). Thorn-shaped astrocytes are also observed subpial and periventricular regions, an interesting link to ARTAG (McKee et al., 2016; Kovacs et al., 2020).

5 Do astrocytes contribute to tau pathology spread?

Neurofibrillary tangles have long been acknowledged to follow a stereotypical temporospatial pattern of spread from the entorhinal cortex as AD progresses (Braak et al., 2011). Recent evidence indicates that differences in the tau species that deposit in characteristic tau lesions may confer specific neuronal vulnerabilities and/or prion-like spread of tau (Clavaguera et al., 2013; Dujardin et al., 2020). Mouse models that express wild-type 3R and 4R human tau isoforms in appropriate ratios recapitulate the same cell type vulnerabilities that typify human tauopathies when injected with human tau extracts, including the development of tufted astrocytes in PSP tau-injected mice, and astroglial plaques in CBD tau-injected mice (He et al., 2020). These data raise the possibility that astrocytes actively contribute to the spread of pathological forms of tau, particularly in PSP and CBD. That tau spreads in a prion-like manner trans-synaptically along anatomical connections was elegantly shown in transgenic mice in which mutant human (P301L) FTLD-causing tau expression was restricted to layer II neurons in the entorhinal cortex. Following local tau aggregation, tau "seeds" were found to spread to the hippocampus and onwards as mice aged (De Calignon et al., 2012; Liu et al., 2012). Notably, PHF1-positive tau was detected in GFAP-positive astrocytes in the hippocampus of older mice, suggesting that astrocytes internalise and may contribute to tau spread (De Calignon et al., 2012) (Figure 1).

Heparan sulfate proteoglycans (HSPGs) are a well-conserved group of proteoglycans expressed on the cell surface of astrocytes and neurons (Turnbull et al., 2001; Sarrazin et al., 2011) that mediate targeted endocytosis (Turnbull et al., 2001), including that of purified prion proteins *in vitro* (Schonberger et al., 2003; Horonchik et al., 2005). HSPGs were recently shown to interact with protein aggregates including α-synuclein, Aβ and tau (Kanekiyo et al., 2011; Holmes et al., 2013; Ihse et al., 2017). HSPGs regulate the uptake of synthetic tau fibrils (Holmes et al., 2013) and human brain-derived tau (Puangmalai et al., 2020) in human immortalised cell lines and mouse primary neuronal cultures. HSPGs vary in the length of their glycosaminoglycan chains and sulfation patterns, properties that are important for tau uptake in human embryonic kidney cells (Stopschinski et al., 2018) and human iPSC derived neurons (Rauch et al., 2018). Interestingly, tau fibrils are efficiently internalised in a HSPG-dependent manner by primary astrocytes exogenously expressing transcription factor EB (TFEB), a master regulator of lysosomal biogenesis (Martini-Stoica et al., 2018). In contrast, monomeric tau appears to be taken up by astrocytes using an HSPG-independent mechanism (Perea et al., 2019). Together this suggests that multiple mechanisms are involved in tau

uptake by astrocytes, that may be specific to tau aggregation state or conformation, as well as the HSPG profile of the cell type (Tselnicker et al., 2014).

HSPGs can also partner with cell surface receptors to mediate the intake of protein aggregates. For example, HSPGs interact with members of the low-density lipoprotein receptor (LDLR) such as LRP1, to facilitate Aβ uptake and degradation by astrocytes (Kanekiyo and Bu, 2014; Liu et al., 2017). Knockdown of LRP1 was recently shown to block the uptake of monomeric and oligomeric tau in a human neuroglioma cell line, and partially inhibit uptake of sonicated tau fibrils (Rauch et al., 2020), warranting further investigation into how astrocytic LRP1 may mediate tau uptake and spread in tauopathies.

Astrocytes are an integral part of the glymphatic system of the brain, a clearance system of soluble proteins and solutes. The astrocytic water channel aquaporin-4 (AQP4), expressed at the astrocyte end feet, facilitates this process and is important for Aβ clearance (Benarroch, 2007; Iliff et al., 2012). Disruption to AQP4 may also contribute to tauopathy progression. In a mouse model of CTE, knockout of AQP4 exacerbated neurofibrillary tau pathology and neurodegeneration (Iliff et al., 2014). Distinct phosphorylation marks in AQP4 have been reported in human post-mortem ARTAG samples relative to controls (Ferrer et al., 2018) that are suggested to increase water permeability of AQP4. However, the functional implications of these modifications in ARTAG remain to be explored (Han et al., 1998; Kitchen et al., 2015). A recent transcriptional analysis of cognitively-impaired subjects and controls showed that components of the dystrophin-associated complex, which anchors AQP4 at the perivascular astrocytic end foot, are associated with phosphorylated tau levels in the temporal cortex (Simon et al., 2018). This analysis also revealed other astrocyte endfoot candidate genes that significantly correlate with temporal cortex tau pathology. The authors speculate that endfoot functions of astrocytes may play a role in the accumulation of tau aggregates throughout the brain. Although AQP4 might contribute to the clearance of aberrant proteins early in the disease process, this function could become impaired at later stages, hindering the clearance of pathogenic tau.

6 Tau effects on astrocyte function

In addition to potential roles in tau spread, internalisation of pathological forms of tau has been shown to disrupt a myriad of astrocytic functions, central for the maintenance and support of neurons. Oligomeric tau uptake alters calcium signalling and gliotransmitter release (e.g. ATP) via Ca^{2+}-dependant mechanisms to disrupt post-synaptic currents and downregulate pre- and post-synaptic markers in neuronal-astrocyte co-cultures (Piacentini et al., 2017), together suggesting that tau-induced changes to astrocyte function are toxic to neighbouring neurons, at least *in vitro*. Astrocytes isolated from a transgenic tauopathy model (P301S) expressing a 4R mutant tau isoform also acquired early functional deficiencies that impaired their ability to support neurons in culture (Sidoryk-Wegrzynowicz et al., 2017). Astrocytes from mouse models of tauopathies also show altered expression of neuronally regulated genes (Hasel et al., 2018), indicating that the accumulation of abnormal tau species is sufficient to drive transcriptional and likely functional changes in astrocytes, via altered neuron-astrocyte interactions. In addition, human astrocytes differentiated from iPSCs harbouring FTD-causing *MAPT* mutations display an increased vulnerability to oxidative stress and elevated protein ubiquitination, alongside disease-associated transcriptomic alterations (Hallmann et al., 2017).

The immune-related functions of astrocytes are a major contributor to neuroinflammatory response that directly alter neuronal integrity in neurodegenerative diseases (Sofroniew and Vinters, 2010). In

particular, the complement cascade, which also involves microglia, has an important role in the accumulation of beta-amyloid pathology (Veerhuis et al., 2011; Lian et al., 2016). C3 is a major component of the complement cascade and is highly expressed in reactive astrocytes (Liddelow et al., 2017). C3, as well as its downstream receptor C3aR1, that is mainly expressed by microglia, (Zhang et al., 2014), is upregulated in postmortem tauopathy brain and correlates with cognitive decline during disease progression (Litvinchuk et al., 2018). Levels of C3 also correlate with tau amounts in AD CSF (Wu et al., 2019). Ablation of C3aR or C3 in mouse models of tauopathy reversed neuronal loss and neurodegeneration (Litvinchuk et al., 2018; Wu et al., 2019), alongside reduced numbers of GFAP-reactive hypertrophied astrocytes being apparent upon C3aR knockout (Litvinchuk et al., 2018). These data indicate that complement activation downstream of astrocyte reactivity may be an important driver of tauopathy.

Astrocytes, together with microglia, are also hypothesized to induce synaptic loss and neurotoxicity in tauopathies, as they do during development (Chung et al., 2013), through dysregulated synaptic pruning (Henstridge et al., 2019). Sleep deprivation is common in AD (Noble and Spires-Jones, 2019), where it is believed to be both a cause and consequence of neurodegenerative changes (Noble and Spires-Jones, 2019). Sleep deprivation leads to enhanced tau release and spread (Holth et al., 2019), alongside astrocyte-mediated synapse elimination (Bellessi et al., 2017). It is therefore possible that astrocyte engulfment of tau-containing synapses may be one route by which astrocytes contribute to tau spread in AD.

Ultimately, cross-talk between astrocytes and microglia forms part of a complex innate immune response that may be exacerbated during tauopathies in response to protein aggregates. Deeper investigation of these pathways may reveal novel targets that can be exploited to slow or halt disease progression.

7 Discussion

Recent evidence has highlighted that altered astrocyte functions have detrimental consequences for neurons and may be a driver of neurodegenerative diseases. Astrocytes are closely associated with the accumulation of pathological forms of tau in tauopathies. There is some evidence that astrocytes internalise tau aggregates, via mechanisms that are not yet fully understood, and contribute to tau pathology spread across the brain and tau aggregate clearance via the glymphatic system. However, astrocytes show significant regional heterogeneity and more work is needed to better understand the contribution of different astrocyte subtypes in affected brain regions at different disease stages. Such understanding may aid in the development of astrocyte-targeted therapies for tauopathies. Astrocyte-targeted therapeutic approaches have been well described elsewhere including by Sadik and Liddelow (2019), and could include antagonists that prevent tau uptake by astrocytes to reduce tau spread, agents that prevent the release of neurotoxic astrocyte secretions or their uptake by neurons, or therapies that restore physiological astrocyte functions including their trophic support for neurons and synapses, maintenance of the blood brain barrier, and roles in the glymphatic clearance of protein aggregates.

7 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8 Author Contributions

MJR, PBL, LJ, BGP-N and WN wrote and edited the manuscript.

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11 Figure legends

Figure 1. Astrocytic mechanisms that may contribute to spread of tau pathology. 1) Tau monomers and aggregates are released from neurons via various mechanisms, including from the pre-synapse, 2) Astrocytes have specific HSPGs and receptors such as LDR1 that may mediate the uptake of tau aggregates, 3) These aggregates may be internalised and processed by various mechanisms, include lysosomal degradation, 4) Disruption of AQP4 in perivascular astrocytic end-feet may contribute to the disrupted tau clearance and the accumulation of tau aggregates in the CNS.

HSPG, heparin sulfate proteoglycan; LDR1, low density lipoprotein receptor-related protein 1; AQP4, aquaporin-4

652 **12 Tables**

Disease	**PiD**	**PSP**	**CBD**	**AGD**	**GGT**	**ARTAG**	**AD**	**PART**	**CTE**
Common clinical symptoms	Aphasia, several behavioural changes including and personality changes, cognitive changes at later stages of disease.	Balance and motor deficits, dysphagia and aphagia.	Motor problems (often one-sided), aphagia, dysphagia.	Amnestic mild cognitive impairment often accompanied by neuropsychiatric symptoms.	Behavioural changes, mood swings, short-term memory loss.	Often no cognitive impairment or dementia related symptoms. Focal pathology may correlate with specific deficits, especially in the presence of co-pathology.	Dementia; progressive episodic memory deficits; navigational and multi-tasking difficulties; diverse behavioural and personality changes.	Associated with cognitive impairment and mild AD-like symptoms.	Behavioural changes, mood swings, short-term memory loss.
MAPT cause/risk	Mostly sporadic; MAPT mutations (exon 9, 10, 11, 12, 13 and intron 9, 10).	Mostly sporadic, H1/H1c MAPT haplotype increases risk; MAPT mutations (exon 1, 10, and intron 10);	Mostly sporadic; H1 MAPT haplotype increases risk; MAPT mutations (exon 10, 13 & intron 10);	H1 MAPT haplotype may increase risk; MAPT mutations (exon 10)	H1 MAPT haplotype; MAPT mutations (exons 1, 10, 11, intron 10).	*Depending on sub-type and classification*	Mostly sporadic; APP, PSEN1, PSEN2; No MAPT mutations	*Depending on sub-type and classification*	*Unknown* (external causes)
Primary tau isoforms that	3R	4R	4R	4R	4R	4R	3R & 4R	3R & 4R	3R & 4R

accumulate in lesions									
Affected brain regions	Frontal and temporal cortices.	Precentral cortex, subcortex (globus pallidus, substantia nigra, pontine nuclei, subthalamic nuclei).	Frontal and temporal cortices.	Medial temporal lobe.	Frontal, precentral and/or temporal cortices.	Grey and/or white matter, perivascular, subpial, subependymal.	Entorhinal cortex and hippocampus, spreading to most regions except the cerebellum.	Entorhinal cortex, hippocampus.	Begins focally at depths of cerebral sulci, spreads widely to frontal temporal lobes.
Hallmark astrocytic tau pathology	Ramified	Tufted	Astrocytic plaques	Thorn-shaped & granular fuzzy/bush-like	Globular inclusions	Thorn-shaped & granular fuzzy	*None*	*None*	Astrocytic tangles and some thorn-shaped astrocytes.
Cellular localisation of astrocytic tau inclusions	Asymmetric 3R (predominant) or 4R tau inclusions in cell bodies & proximal processes.	Symmetric 4R tau inclusions in proximal processes.	4R tau in distal processes and end feet; thread-like processes are also common.	4R tau inclusions and diffuse staining in cell bodies & proximal-distal processes.	4R globular tau in cell bodies & proximal processes.	4R tau inclusions and diffuse staining in cell bodies & proximal processes.	*n/a*	*n/a*	Irregular p-tau lesions (around small vessels).

References	Forrest et al., (2018; 2019); Dickson, (2001; 2011); ; Josephs et al., (2011); Ferrer et al., (2014).	Forrest et al., (2018; 2019); Cairns et al., (2007); Kovacs and Budka, (2010).	Forrest et al., (2018; 2019); Dickson et al., (2011); Ling et al., (2016).	Forrest et al., (2018; 2019); Botez et al., (1999); Saito et al., (2004).	Forrest et al., (2018; 2019); Ahmed et al., (2013).	Forrest et al., (2018; 2019); Kovacs et al., (2016, 2017, 2018, 2020).	Guerreiro et al., (2012); Braak and Braak, (1991); Braak et al., (2011).	Forrest et al., (2018; 2019); Crary et al., (2014); Jellinger et al., (2015).	Forrest et al., (2018; 2019); Stein et al., (2014); McKee et al., (2015; 2016).

Table 1: Overview of the main clinical, genetic, molecular, and pathological features of tauopathies, including description of astrocyte abnormalities.

PiD, Pick's disease; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; AGD, argyrophilic grain disease; GGT, globular glial tauopathy; ARTAG, age-related tau astrogliopathy; AD, Alzheimer's disease; PART, primary age-related tauopathy; CTE, chronic traumatic encephalopathy; 3R, 3-repeat tau; 4R, 4-repeat tau.