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Tauopathies as clinicopathological entities☆

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ABSTRACT

Tauopathies are a class of neurodegenerative disorders characterized by neuronal and/or glial inclusions composed of the microtubule-binding protein, tau. Several lines of evidence suggest tau aggregation is central to the neurodegenerative process in tauopathies. First, recent animal and cell model studies find abnormally-modified tau alone may be transmitted between adjacent neurons and spread to anatomically connected brain regions to recapitulate human disease. Further, staging efforts in human autopsy cases suggest a sequential distribution of tau aggregation in the central nervous system that could reflect this observed cell-to-cell transmission of pathogenic tau species in animal models. Finally, pathogenic mutations in the *MAPT* gene encoding tau protein cause hereditary forms of tauopathy.

Clinically, tauopathies can present with a range of phenotypes that include both movement- and cognitive/behavioral-disorders (i.e. frontotemporal dementia spectrum disorders) or non-specific amnestic symptoms in advanced age. A major limitation is that current clinical diagnostic criteria for these disorders do not reliably differentiate underlying tauopathy from other neurodegenerative diseases, such as TDP-43 proteinopathies. Thus, current research efforts are focused on improving the ante mortem diagnosis of tauopathies, including pre-clinical stages of disease, as many therapeutic strategies for emerging disease-modifying therapies focus on preventing abnormal folding and spread of tau pathology.

1. Introduction

Age-associated neurodegenerative diseases are characterized by specific key protein inclusions, accompanied with neuronal loss and gliosis. A major class of neurodegenerative diseases, collectively known as tauopathies, are characterized by intra-cellular inclusions composed of abnormally-modified microtubule-binding protein, tau, at autopsy. Primary tauopathies are a major class of Frontotemporal Lobar Degeneration (FTLD) neuropathology (i.e. FTLD-Tau) [1] and can present clinically with several forms of Frontotemporal Dementia (FTD) clinical syndromes (i.e. behavioral-variant FTD, bvFTD [2]; primary progressive aphasia, PPA [3]), including atypical dopaminergic-resistant Parkinsonian syndromes with prominent extra-pyramidal symptoms (i.e. progressive supranuclear palsy syndrome, PSPS [4]; corticobasal syndrome CBS [5]). For a comprehensive review of clinicopathological correlations in FTLD-Tau from large autopsy series please see Ref. [6]. Other primary tauopathies can be associated with mild or poorly differentiated amnestic symptoms late in life [7,8]. Finally, Alzheimer's disease (AD) neuropathology includes significant neurofibrillary tau neuropathology in addition to amyloid-beta (Aβ) plaques and can be considered a secondary or non-primary tauopathy, although these classifications are currently a matter of considerable debate. AD neuropathology can also have atypical clinical presentations as FTD clinical syndromes. These discordant relationships pose a significant problem for accurate diagnosis and the gold standard is neuropathological examination at autopsy; thus, tauopathies are best viewed as clinicopathological entities, that is, the underlying neuropathological substrate and the resultant clinical syndrome.

This view is important in light of emerging evidence from *in vivo* models of tauopathies. Recent data from several groups find that tau may undergo a self-templating process to recruit normal soluble tau to form and propagate insoluble tau fibrils between neurons within the CNS in transgenic animals or between neurons in cell culture systems (For a comprehensive review of transmission studies please see Ref. [9]). Notably, intracerebral injections of synthetic tau fibrils alone into transgenic mice found a time- and

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dose-dependent sequential topographical spread of tau aggregations in the CNS [10]. These animal model findings are similar to the non-random sequential patterns of tau deposition in human diseases such as Alzheimer's Disease (AD), originally described by Braak and colleagues in the early 1990s [11], and more recently observed in a primary tauopathy, Pick's disease (PiD) (Irwin DJ, Brettschneider JB, McMillan CT, Cooper F, Olm C, Arnold SE, Van-Deerlin VM, Seeley WW, Miller BL, Lee VMY, Grossman M and Trojanowski JQ, 2015 unpublished data). Further, intracerebral injections of tau lysates from different forms of tauopathy into transgenic mice results in similar inclusion morphologies in recipient animals to human disease, which could suggest abnormally folded tau could exist as different strains [12]. Tau transmission in these studies is similar to the observations in human prion disease, where misfolded PRP^{SC} protein seeds fibrillization of native PRP^{C} to cause the spread of misfolded prion throughout the CNS accompanied by neurodegeneration; however in contrast to human prion disease there is no current definitive evidence of infectivity (i.e. transmission of disease) between humans or non-human primates for AD or FTLD-Tau, even in extreme circumstances such as exposure to human CNS tissue [13].

These emerging findings for transmission and propagation of pathogenic tau aggregations in tauopathies suggest that slowing or halting this process may be an important strategy for therapeutic developments for tauopathies. Indeed, there are several approaches possible for potential therapies targeting tau [14] and clinical trials for tau-directed immunotherapy are currently underway (NCT02460094, NCT02494024). Thus, accurate ante mortem diagnosis of tauopathies is critical for the evaluation of these disease-modifying therapies targeting tau. This review will describe the major classes of tauopathy and key clinicopathological relationships to emphasize the importance of ante mortem diagnosis of these conditions.

2. Neuropathologic subtypes and clinicopathological correlations

2.1. General features of tauopathies

The tau protein is normally found in the cytosol of neurons and glial cells in the central nervous system (CNS) and its function is to bind microtubules to stabilize the cell cytoskeleton (For comprehensive review on tau please see Ref. [14]). Tau exists in 6 isoforms based on the presence of 0, 1 or 2 sequence inserts in the amino-terminus of the protein and inclusion or exclusion of the second of four microtubule-binding potential repeat domains (MTBD) coded by exon 10. Tauopathies are classified by the predominance of tau isoforms found in cytoplasmic inclusions: those with inclusions predominantly composed of tau with 3 MTBDs (i.e. 3R-tauopathies), those with predominantly 4 MTBDs (i.e. 4R-tauopathies) or an equal ratio of 3R:4R tau (Fig. 1). Tau normally exists in an equal ratio of 3R:4R tau in non-disease states. Tau undergoes several post-translational modifications, most notably phosphorylation at multiple serine and threonine sites, which regulates microtubule binding under normal conditions. In pathological conditions of tauopathy tau is hyperphosphorylated. Other modifications include, acetylation, nitration, glycation, conformational change and C-terminal truncation. Some of these modifications are found only in insoluble tau aggregations associated with disease and not in healthy tissue, such as acetylation of tau at lysine 280 (ac-K280) in the second MTBD of 4R tau [15,16]. A hypothetical sequence of tau modifications has been proposed to occur during the process of tangle formation. This sequence of modifications is based on the abundance or absence of specific tau epitopes in neurofibrillary tau pathology seen in the hippocampus across mild to severe AD cases [17,18]. Interestingly, tauopathies universally express “early tau modifications” (i.e. phosphorylation, conformational change), while later-occurring modifications (i.e. C-terminal truncation) appear to be more prominent in extracellular ghost tangles from degenerated neurons seen only in AD [16,18]. Further, reactivity to amyloid-binding dyes, such as Thioflavin-S (ThS) or silver impregnation methods, which bind to more fibrillary tau deposits vary among tauopathies [16,19,20]. Tauopathy transmission data support these hypotheses as more mature tau pathology induced from intracerebral injections of tau fibrils are both ThS and ac-K280 positive [10]. Ultrastructural analysis finds AD tau neurofibrillary pathology is composed of tightly paired-helical filaments, while other tauopathies may have less compact straight or twisted ribbon filament [8]. Finally tauopathies vary in the cell types (i.e. neurons or glia) and anatomical regions (i.e. limbic/neocortex, basal ganglia and brainstem) most vulnerable to tau-mediated neurodegeneration.

2.2. FTLD-tau with MAPT mutation

There are over 40 known pathogenic mutations in the *MAPT* tau gene (chromosome 17) which result in tauopathy (i.e. FTLD-Tau with *MAPT* mutation) (For comprehensive review of specific *MAPT* mutations please see Ref. [21]). *MAPT* pathogenic mutations are thought to cause disease by either 1) inhibiting the normal microtubule-binding function of tau, 2) promoting tau protein aggregation or 3) affecting the splicing of exon 10 to result in imbalances between 3R/4R tau isoforms. As such, specific neuropathological findings (e.g. tau isoform predominance, inclusion morphology/ultrastructure) vary for each specific mutation, but universally include neuronal and glial tau inclusions together with neurodegeneration throughout the CNS, with a particular propensity for frontal and temporal neocortex and limbic structures [21]. The majority of cases are negative for ThS and those with 4R tau pathology reactive for ac-K280 [19]. Clinically FTLD-Tau with *MAPT* mutations may present with FTD behavioral (i.e. behavioral-variant FTD; bvFTD) and/or language syndromes (i.e. primary progressive aphasia; PPA) and often times have extra-pyramidal features (Parkinsonism). The majority of mutations are inherited in an autosomal dominant pattern and usually with a high-degree of penetrance. The age of onset varies by specific mutation, but in general disease onset is between ages 45–65 with a wide variation in disease duration (average ~10 years); although cases in the second and third decade and also eighth decade may occur.

2.3. 4R tauopathies: progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a 4R tauopathy characterized by globose tau inclusions in brainstem and subcortical neurons, in addition to glial “tufted astrocytes” and neuronal tangles in grey matter and oligodendrocytic “coiled bodies” in the white matter of the neocortex [8,16]. There is prominent tau pathology in the brainstem, sub-thalamic nucleus and dentate nucleus of the cerebellum. PSP tau pathology is mildly reactive for Thioflavin-S and robustly reactive for ac-K280 [16]. The most common clinical presentation is PSP syndrome (PSPS), an age-associated atypical Parkinsonian syndrome characterized by prominent axial rigidity and poor response to dopaminergic therapy. The clinical diagnosis of PSPS, especially clinical findings of supranuclear gaze palsy and early postural instability/falls, are very specific for underlying PSP tauopathy [4]; however, PSPS is not sensitive to detect all cases of PSP neuropathology, as patients with clinical features of the non-fluent variant of PPA (naPPA), corticobasal syndrome (see below) or bvFTD (reviewed in Ref. [6]). Further, cognitive and behavioral features of PSPS are being increasingly

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