

Primary age-related tauopathy (PART): a common pathology associated with human aging

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Abstract We recommend a new term, “primary age-related tauopathy” (PART), to describe a pathology that is commonly observed in the brains of aged individuals. Many autopsy studies have reported brains with neurofibrillary tangles (NFTs) that are indistinguishable from those of Alzheimer’s disease (AD), in the absence of amyloid (A β) plaques. For these “NFT+/A β –” brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (bulb and cortex). Symptoms in persons with PART usually range from normal to amnesic cognitive changes, with only a minority exhibiting profound impairment. Because cognitive impairment is often mild, existing clinicopathologic designations, such as “tangle-only dementia” and

“tangle-predominant senile dementia”, are imprecise and not appropriate for most subjects. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be specifically identified pre-mortem at the present time. Improved biomarkers and tau imaging may enable diagnosis of PART in clinical settings in the future. Indeed, recent studies have identified a common biomarker profile consisting of temporal lobe atrophy and tauopathy without evidence of A β accumulation. For both researchers and clinicians, a revised nomenclature will raise awareness of this extremely common pathologic change while providing a conceptual foundation for future studies. Prior reports that have elucidated features of the pathologic entity we refer to as PART are discussed, and working neuropathologic diagnostic criteria are proposed.

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Introduction

We propose a new term, “primary age-related tauopathy” (PART), to describe a pathologic continuum ranging from focally distributed neurofibrillary tangles (NFTs) observed in cognitively normal aged individuals, through the pathology observed in persons with dementing illnesses that have been referred to as “tangle-predominant senile dementia” (TSPD), “tangle-only dementia”, “preferential development of NFT without senile plaques”, and “senile dementia of the neurofibrillary tangle type” (SD-NFT), among other names. Here we explain the need for introducing this term, reviewing the relevant studies in the clinical and pathologic literature. We conclude with new proposed working guidelines for the neuropathological classification of subjects with PART.

The main reasons for proposing this new terminology are to provide a conceptual framework for studying PART, to facilitate communication among pathologists, clinicians, and researchers, and to draw attention to this entity, which is often overlooked. Another motivation, as with the recent National Institute on Aging-Alzheimer’s Association diagnostic criteria for Alzheimer’s disease (AD) [64,

102], is to “disentangle” pathologic classification from clinical diagnosis for a given patient. In the case of PART, the separation of clinical information from the pathological diagnosis is especially necessary, because the term “dementia”, as in “tangle-only dementia”, implies a multi-domain cognitive impairment with a profound decrease in the ability to perform activities of daily living, both of which are absent in the majority of persons with PART [65, 66, 107, 125, 142]. Practicing neuropathologists will benefit from the revised terminology because many are reluctant to apply the clinical term “dementia” to a pathologic diagnosis when dementia was not documented clinically or when knowledge of the clinical history is limited. Also, there have been recommendations to lessen the use of labels such as “dementia” and “senile” partly due to pejorative implications [139] and because the terms are considered to be imprecise [24].

Patients with mild-to-moderate AD-type neurofibrillary degeneration in the medial temporal lobe, but lacking A β plaques, have been described in European, Japanese, North and South American cohorts [2, 3, 14, 51, 52, 58, 69, 72, 79, 81, 82, 126, 142, 147, 149, 151]. NFTs are practically universal in older persons’ brains [22, 30, 108, 132], and are also observed in a more limited distribution in many younger individuals [30, 32, 42]. Cases at the more severe end of the pathologic spectrum (Braak stages III–IV)

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lacking A β plaques were observed in 2–10 % of brains in large autopsy series that included community-based sampling [89, 94, 107, 125]. These pathologic changes were more prevalent in a few autopsy series drawing from memory disorder clinics [128, 129]. The theoretical and practical implications of these findings remain controversial [9, 15, 29, 107]. Differences in nomenclature, study design (including cohort recruitment methods) variable sensitivity in detecting pathologic changes, and conceptual interpretations have fueled uncertainty. A more specific and ultimately useful term for neuropathologic diagnoses is required, drawing from an expanding research corpus.

Clinical features

Published data indicate that severe PART can be associated with memory loss in aging [66, 107]. However, the high prevalence of comorbid brain diseases in elderly individuals make clinicopathologic correlations challenging in this population [76, 80, 108, 109, 117, 125], and the entire clinicopathologic spectrum of PART has yet to be systematically characterized. Most relevant prior studies have either focused on the most severe cases with TPSD or have investigated the associations between medial temporal lobe or

brainstem tau pathology related to AD [5, 6, 11, 12, 19, 48, 49, 55, 56, 79, 133, 134, 144]. A subset of patients with PART (previously referred to as SD-NFT, TPSD, etc.) displays marked clinical impairment in the absence of any other recognizable substrate for dementia [14, 21, 39, 60, 66, 72, 99, 142]. The average age of death is generally higher for these patients than those with AD pathology [37, 79, 107]. Whereas cognitively impaired subjects with PART often carry a clinical diagnosis of possible or probable AD [115], the coexistence of PART and AD in aging is an inevitable complicating factor [153]. A recent analysis of the National Alzheimer's Coordinating Center (NACC) autopsy database [16] found that ~14 % of subjects clinically diagnosed with mild-to-moderate probable AD had no or sparse neuritic plaques [128]. Here we provide additional data from the NACC database that underscore characteristics of PART: the pathology is common and Braak stage "0" is relatively unusual in older individuals; there is an absence of an association between PART and *APOE* genotype; and, the more severe PART pathology is associated with a higher age of death and lower scores on cognitive tests (Table 1).

The application of imaging and CSF biomarkers has given a novel perspective on the prevalence and associated clinical features of neurodegenerative processes that undoubtedly

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Table 1 Clinical features of primary age-related tauopathy (PART)

	Amyloid plaque density	Braak stage				
		0	I	II	III	IV
Number of subjects						
PART, definite	None	11	22	25	15	15
PART, possible	Low	4	16	27	16	31
–	Mod	2	11	15	32	50
–	High	3	7	10	39	83
Age at death (average)						
PART, definite	None	81.3	82.4	88.5	88.4*	92.0***
PART, possible	Low	88.4	80.4	84.7	89.7*	87.6*
–	Mod	89.0	80.2	87.4*	84.9	86.5
–	High	77.0	84.9	86.7	85.3	84.6
Final MMSE scores						
PART, definite	None	28.0	28.4	26.5	25.1***	24.3***
PART, possible	Low	28.5	25.8	24.4	24.6	21.9*
–	Mod	26.5	26.8	27.3	23.2*	19.8*
–	High	25.5*	24.5	27.9*	21.2*	18.8***
APOE ε4 positive (%)						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	35.5*
–	Mod	0.0	36.4	13.3	34.4*	50.0*
–	High	66.7*	28.6	50.0*	33.3*	56.6***

Patients from the National Alzheimer's Disease Coordinating Center (NACC) Neuropathology Database who died after 2005, with Mini-Mental State Examination (MMSE) during life, but no evidence of severe AD, frontotemporal lobar degeneration, triplet repeat disorder, amyotrophic lateral sclerosis, or other known neurological syndrome at autopsy. A total of 434 individuals met inclusion criteria. Statistical comparisons versus Braak NFT stage 0 cases. Age and MMSE were assessed with one-way ANOVA; *APOE* was assessed with Fisher's exact test

* $p < 0.05$ as individual test

** $p < 0.05$ after Bonferroni–Holm correction for multiple comparisons

*** Combining Braak III/IV comparing to Braak 0 leads to $p = 0.003$ (Student's *t* test)

include PART. Biomarker-based clinical research supports the claim, initially made based on the autopsy studies of putatively cognitively intact people [36, 88] and of persons with mild cognitive impairment (MCI) [83, 93, 113], that tauopathy in the absence of A β -type amyloidosis is common. Reported biomarkers include CSF A β (1–42) or positron emission tomography (PET) imaging for A β pathology and CSF tau or phospho-tau, structural MRI, and PET (including fluorodeoxyglucose PET) for neurodegeneration. The abnormalities of the neurodegeneration biomarkers have generally been defined relative to levels seen in AD. It appears that roughly a quarter of cognitively normal elderly individuals have abnormal neurodegeneration biomarkers in the absence of abnormal brain amyloidosis [86, 87, 143, 145]. This clinical cohort's status has been termed “suspected non-Alzheimer pathophysiology” (SNAP) to distinguish it from persons with A β -type amyloidosis [75, 87]. In persons with amnesic MCI, remarkably, about the same proportion of SNAP cases is found [112, 114]. Although autopsy experience is limited so far in cases with biomarker-defined SNAP,

the prominent involvement of the medial temporal lobe in reported SNAP cases suggests that PART-type pathologic changes may underlie at least a subset of persons with the SNAP biomarker profile in the broader population. A more specific diagnostic classification enables terminology that parallels the recently adopted nomenclature for AD, with a biomarker-positive presymptomatic stage and a symptomatic stage where both biomarkers and clinical phenotype are present [74]. There are ongoing and potential future clinical trials that target either A β - or tau-related pathogenic mechanisms. PART and AD may well respond differently to those therapeutic interventions [23], which underscore the importance of harmonizing clinical decisions with data that were previously obtained in high-quality autopsy series.

Neuropathologic changes

Gross examination of the brain of subjects with PART may show no obvious differences from those deemed

“normal for age”. In other individuals with PART, there may be mild-to-moderate diffuse atrophy of the neocortex, and medial temporal lobe atrophy may be pronounced in persons with dementia (Fig. 1) [110, 122]. Immunohistochemistry reveals telencephalic NFTs emerging most consistently in the medial temporal lobe, particularly the hippocampal formation and adjacent regions (Fig. 1b–d). Abnormal tau-immunoreactive inclusions are most prominent in neurons (Fig. 2). Subcortical NFTs can be observed even in teenage years in the locus coeruleus [9, 30, 41, 42, 131], so this process is not necessarily limited to individuals of advanced age. NFTs may also be seen in the amygdala, nucleus basalis of Meynert, nucleus accumbens, hypothalamus, thalamus, olfactory system (bulb and cortex), dorsal raphe nucleus, and medulla oblongata [7, 8, 53, 107, 141]. While NFTs at all stages of evolution can be seen in PART, individuals with cognitive impairment often have abundant extracellular, so-called “ghost”, tangles [110, 122].

The only existing grading system that applies to PART is Braak neurofibrillary staging [26, 28, 32]. The pathologic continuum of PART includes pretangle or cortical pretangle (up to Stage Ib), entorhinal (I–II), or limbic (III–IV) Braak stages [25, 27, 28]. Theoretically, given experimental findings that tau pathology might be propagated transsynaptically [34, 35, 38, 46, 47, 57, 91], it is notable that

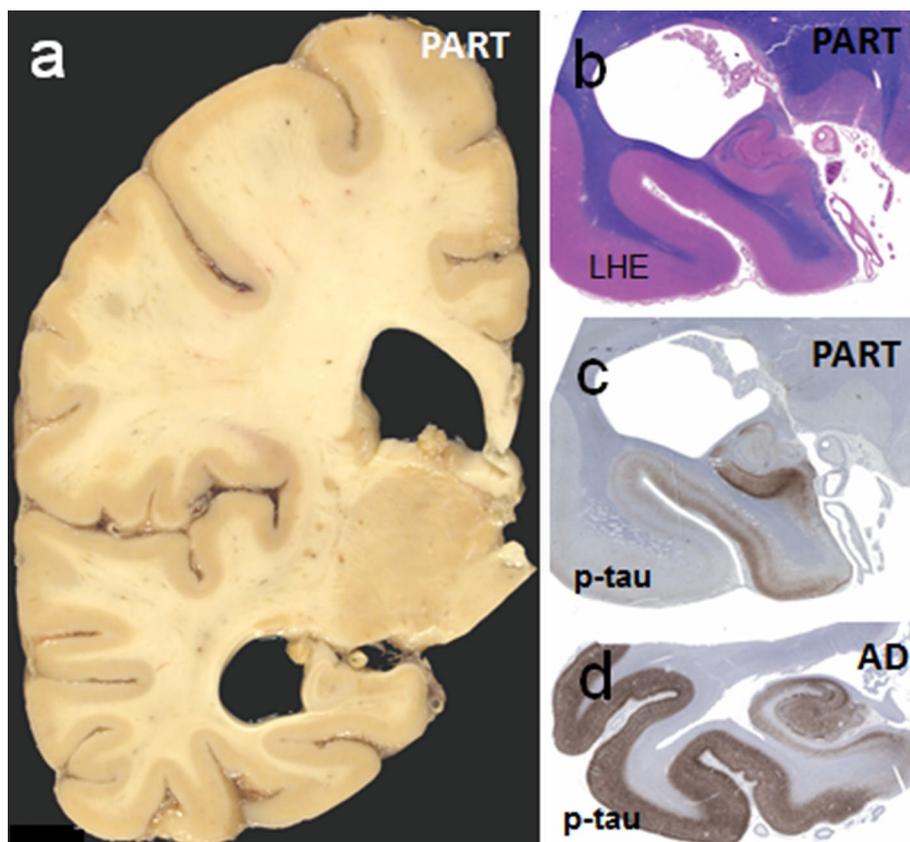
PART-type pathology generally does not progress to the isocortical Braak stages (i.e., V–VI), remaining relatively restricted neuroanatomically even in the oldest-old subjects with limited extension beyond the temporal neocortex to other neocortical regions [73, 148].

The neurofibrillary changes in PART resemble those in AD brains (Fig. 3). Immunohistochemical and biochemical studies have found that NFTs in PART, as in AD, contains accumulation of both 3-repeat (3R) and 4-repeat (4R) tau isoforms (Fig. 3a–c) [70, 79, 122, 130]. In AD NFTs, electron microscopy has revealed predominantly paired helical filaments (PHFs), which are considered a disease hallmark [85, 119, 146]. The tau fibrils in brains with PART pathology also display a typical PHF morphology (Fig. 3d) [67, 72, 122]. These observations are not unique to PART and the pathologic overlap requires further consideration.

Differentiating PART from other neurodegenerative diseases

A synthesis of previously reported observations exposes an apparent paradox: the NFT is one of the two defining pathological hallmarks of AD, the other is the A β plaque. However, AD-type NFTs are almost ubiquitously observed in older persons' brains, even in the absence of A β plaques

Fig. 1 Primary age-related tauopathy (PART): gross pathology and low-power photomicrographs. **a** A formalin-fixed left hemisphere from a 103-year-old woman reveals enlargement of the inferior horn of lateral ventricle and severe medial temporal atrophy. Only mild neocortical atrophy is present. **b** A Luxol fast blue-counterstained hematoxylin–eosin section (LHE) shows atrophy of the medial temporal lobe. **c** Phospho-tau (p-tau; AT8)-immunolabeled sections highlight marked tauopathic changes predominantly in the hippocampus and entorhinal cortex. **d** For comparison, a case with advanced AD demonstrates a more severe tauopathy extending into the temporal neocortex



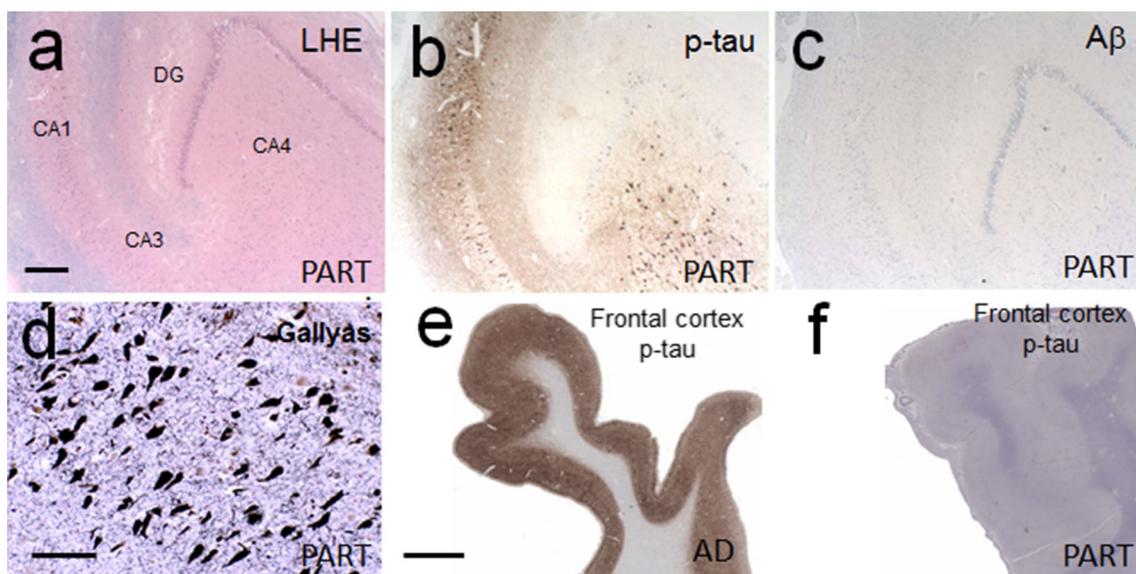


Fig. 2 Primary age-related tauopathy (PART): histopathology. The neuropathology corresponds to Braak stages I–IV, with involvement of the hippocampal formation (**a–c** are nearly serial sections from the hippocampus of the same patient) as shown with Luxol fast blue-counterstained hematoxylin–eosin (LHE) (**a**), and p-tau (AT8) immunohistochemistry (**b**). However, unlike cases with AD, A β immunohistochemistry (**c**) shows minimal or no staining. Gallyas silver impregnation reveals many “ghost tangles” in the hippocam-

pal formation (**d**), here without amyloid plaques. A key difference between AD and PART pathology is that, by definition, advanced AD (**e**) shows extensive hyperphosphorylated tau (p-tau) in neocortical areas such as the prefrontal cortex (Brodmann area 9), whereas PART pathology spares the neocortex (**f**). Scale bar in **a** 1 mm for (**a–c**), scale bar in **d** 100 μ m, and scale bar in **e** 5 mm for (**e**, **f**). CA1–4 denote the hippocampal subfields, DG dentate gyrus

or features of other classifiable tauopathies. Because there are pathologic features in common with AD, some investigators may consider PART a subset of AD or an early stage of AD. Indeed, NFTs in the brainstem of younger adults show features in common with the pathological processes of AD [31]. Yet clinically and pathologically salient features may differ despite the overlap in pathologies. In comparison to AD, current data suggest that PART typically has a far more limited impact on cognition and develops in persons without A β plaques or biochemical evidence of elevated A β [122]. A diagnosis of AD neuropathologic changes requires at least a minimum threshold level of A β deposition [64, 102]. This criterion is supported by extensive genetic and clinicopathologic observations [108]. There is an accumulating body of evidence suggesting that medial temporal lobe NFTs are involved in at least two common processes, an AD-related process, and a non-AD aging-related process [103, 107]. Supportive evidence comes from genetic studies that show an association between PART and the microtubule-associated protein tau gene (*MAPT*) H1 haplotype [76, 122], whereas there is an absence of an association between PART and the strongest risk factor for AD, the *APOE* ϵ 4 allele [13, 67, 70, 122, 150, 151].

PART cases have likely been reported in autopsy series of SD-NFT, TPSD, tangle-predominant dementia

or tangle-only dementia [10, 14, 17, 43, 79, 98, 106, 110, 122]. These proposed pathologic entities may have included some cases that would now be considered fronto-temporal lobar degeneration (FTLD). TPSD has previously been grouped among FTLD subtypes [33] and there are presumably FTLD-tau subtypes that may overlap with the spectrum of PART even if the pathogenesis is distinct. For example, individuals with germline *MAPT* R406W mutation may present as a temporal lobe predominant tauopathy with similar features to TPSD [63], but the presence of NFTs in the globus pallidus, subthalamic nucleus, substantia nigra, and pons in such cases is reminiscent of PSP. The pattern of tau isoform accumulation associated with PART pathology can also be seen in other tauopathies, including amyotrophic lateral sclerosis/Parkinsonism dementia complex of Guam [61, 111, 123, 124], which, like AD, may also show α -synuclein and TDP-43 pathology [50, 140]. By contrast, PSP and CBD display a predominance of 4-repeat tau isoforms, and Pick disease shows predominantly 3-repeat tau isoforms [4, 44, 79, 90, 138, 152]. Also commonly seen in brains from individuals of advanced age are tau-immunoreactive argyrophilic grains. However, argyrophilic grain disease is a 4R tauopathy featuring CA2 pretangles and dentate granule cell involvement, all acetylated tau-negative, and none of these features are seen in AD/PART [54, 71, 84, 107, 120, 136, 138].

Future studies and unanswered questions

Additional studies are necessary to refine our understanding of PART in the complicated context of the aged human brain. Most fundamentally, the exact clinicopathologic spectrum of PART remains to be definitively characterized. Additional topical questions relate to the “boundary zone” between PART and other tauopathies, especially AD. The precise threshold of A β deposition below which a diagnosis of definite PART is appropriate, and the relative importance of diffuse amyloid and neuritic plaques, require further study. In addition, there is a growing appreciation, not yet incorporated into consensus-based guidelines, that the neuropathology of AD is heterogeneous [2, 18, 20, 59, 62, 76–78, 92, 104, 105, 118, 151]. It is possible that brains with hypothesized hippocampal “localized” [100, 101] or “limbic-predominant” [76, 104, 105, 151] AD subtypes are along a common continuum with PART [76, 79, 105]. The rationale for including extracortical tau pathology in PART is that the pathologies commonly coexist and that brainstem NFTs, if they represent the same process, appear to occur even earlier in human aging [30–32, 53]. In this context, it is also not known whether spinal cord tauopathy is related to PART [40]. More studies will be needed to determine whether there are distinct subtypes of extracortical tauopathy and how these changes relate to AD as well

as PART. There are other conditions besides AD that overlap pathologically with PART. For example, it is notable that chronic traumatic encephalopathy generally presents pathologically as a non-A β tauopathy with features that overlap pathologically with PART [95], and in the future markers may be developed to better discriminate between disorders in which NFTs develop in similar brain areas. Tau-immunoreactive glial pathology is also frequently seen in advanced old age [1, 44, 65, 68, 89, 90, 127]. It is unknown whether the age-related glial tauopathy is associated with mechanisms that also cause PART pathology, but PART appears to be a predominantly neuronal pathology. To enable future studies aimed at addressing the extant unresolved questions, a working diagnostic guideline is required.

Neuropathologic criteria

New criteria are proposed to classify patients with PART for research and potential future clinical purposes (Table 2). PART is defined by AD-type neurofibrillary changes without, or with few, A β plaques as described below. PART can be designated as “Definite” or “Possible” depending on the presence of coexisting neuropathology and many cases will not be gradable due to comorbid pathology. Specifically,

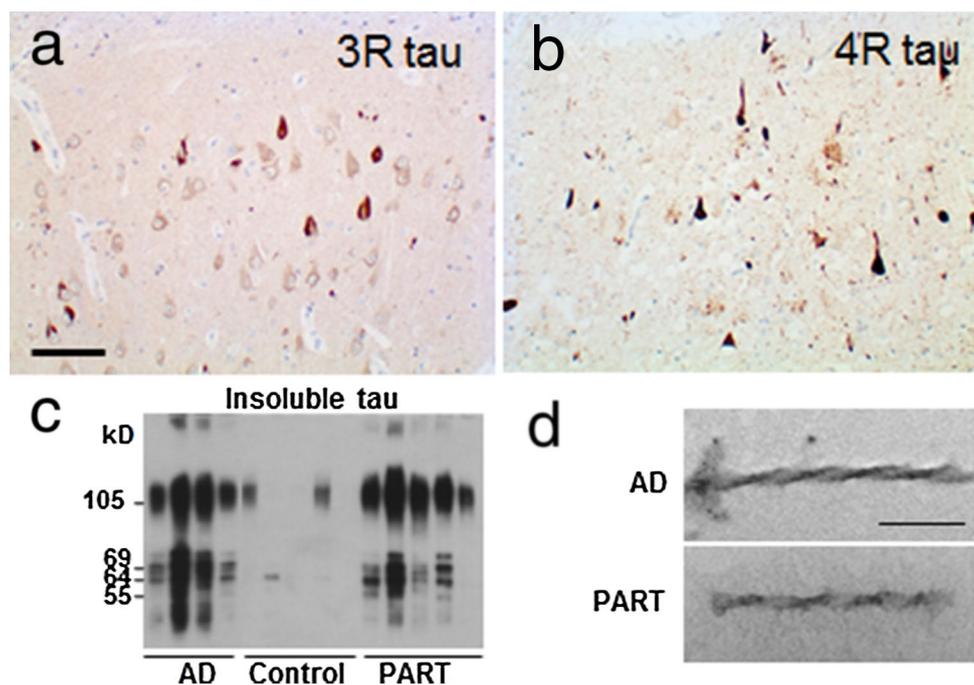


Fig. 3 The NFTs of PART resemble those of AD by immunohistochemistry, biochemistry, and ultrastructure. **a, b** NFTs in PART reveal immunoreactivity with both 3R and 4R anti-tau monoclonal antisera (RD3 and RD4, respectively). *Scale bar* 200 μ m for **a, b**. **c** Immu-

noblot using polyclonal antisera targeting total tau (tau C) shows a banding pattern similar to that in AD (from Ref. [122] with permission). **d** The tau fibrils (paired helical filaments) in PART show similar ultrastructural features and periodicity as in AD. *Scale bar* 100 nm

Table 2 Primary age-related tauopathy (PART): working classification

1. Requires		
NFTs present with Braak stage \leq IV (usually III or lower)		
2. Then subclassify as follows		
Category	Thal A β Phase ^a	Other disease associated with NFT ^b
Definite	0	Absent
Possible	1–2	Absent
Examples		
Primary age-related tauopathy (PART), Definite, Braak stage II		
Primary age-related tauopathy (PART), Possible, Braak stage III, Thal A β phase 2		
3. Ancillary studies (not required)		
Immunohistochemistry: 3R and 4R tau-positive		
Electron microscopy: paired helical filaments present		
Genetics: absence of pathogenic FTLT-tau mutation		

^a See [116, 135]. Laboratories using the CERAD neuritic plaque density score [96, 97] may classify subjects with neuritic plaque frequency of “None” as “Definite” and “Sparse” as “Possible”

^b For example, “progressive supranuclear palsy”, “corticobasal degeneration”, “Pick’s disease”, “frontotemporal lobar degeneration with *MAPT* mutation”, and “chronic traumatic encephalopathy”

neurofibrillary changes may correspond to subcortical pretangle or cortical pretangle (up to Ib), entorhinal (I–II), or limbic (III–IV) Braak stages [25, 27, 28]. In keeping with the current guidelines for AD [64, 102], mild A β plaques defined using the Thal grading system [116, 135, 137], consistent with low AD neuropathologic changes, preclude the diagnosis of “Definite” PART. Some pathologists may prefer the CERAD system for grading neuritic plaque density [96], but the method used must be indicated as it would alter the classification of some subjects. Possible wording for the pathologic diagnoses is provided (Table 2). If both early AD pathology and “Possible” PART pathology are observed, both may be reported diagnostically. The presence of few or moderate argyrophilic grains as assessed with established staging methods [45, 121] does not rule out PART. We emphasize that a pathologic diagnosis of PART does not necessarily indicate that a functional deficit was detected clinically. We also note that Braak stage IV pathology without A β plaques is unusual and in these cases the possibility of a FTLT-tau condition should be considered.

Summary

PART is a common brain pathology relevant to researchers, clinicians, and the broader public. Despite the high prevalence in published brain autopsy series, PART has been difficult to categorize because of the absence of a

well-accepted nosology. We expect that the study of tau biomarkers will broaden the recognition of PART, and improve our understanding of a condition currently known mostly from neuropathologic studies. More studies are needed to better understand the pathogenesis of PART, its relation to other neurodegenerative disorders, and the full clinical spectrum of this common brain disease of aging.

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