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Brain Pathology

LETTER TO THE EDITOR

Primary age-related tauopathy (PART) in the general autopsy setting: Not just a disease of the elderly

Dear Sir,

Primary age-related tauopathy (PART) is an entity recently introduced in an effort to clarify a common finding of neurofibrillary tangles (NFT) consistent with Alzheimer's disease (AD), in a restricted distribution, and in the absence of beta amyloid (Ab) plaques at time of autopsy (1). Subsequent studies have suggested that individuals with the pathologic findings of PART commonly have less clinically significant symptoms of dementia during life, as well as pathologic presentation later in life compared to AD, and have suggested an average age of death in the ninth decade of life as compared to the eighth decade of life with AD (2,3,10). It has been suggested that, in patients with PART, this manifests often as a milder clinical course when compared to those with AD.

First described in 2014 by Crary and colleagues examining a 434 patient National Alzheimer Coordinating Center (NACC) cohort of patients without severe AD or other defined neuropathologic diagnosis at autopsy, PART is defined as AD-type neurofibrillary changes without, or with few Ab plaques (1). Neurofibrillary changes in PART may correspond to subcortical pretangle or cortical pretangle (Ib), entorhinal (I–II), or limbic (III–IV) Braak stages. Furthermore, the NFTs in PART are commonly restricted to the temporal lobes and by definition are not associated with underlying frontotemporal degeneration or chronic traumatic encephalopathy (3).

In order to illuminate the gray area between PART and AD, researchers have suggested subdividing cases into *Definite PART* and *Possible PART*. A patient is diagnosed with Definite PART when there is evidence of AD-like NFT (Braak I–IV) with no evidence of Ab plaques as described by the Thal grading system (Thal score 0). When a patient is found to have AD-like NFTs with mild Ab plaques (Thal score 1–2), consistent with mild AD changes, they are diagnosed with Possible PART (1). Crary and colleagues identified findings consistent with Definite or Possible PART in 182 of their original 434 patient NACC cohort (1).

Critically, researchers have shown that severe cognitive impairment is possible with extensive NFT disease (Braak IV or greater) with no evidence of Ab plaques. Alternatively, severe impairment is also possible in patients with a lower Braak stage with mild (Thal I–II) Ab deposition. This suggests a multifactorial pathway to dementia in this patient population and highlights the need for further study on this topic (1).

To further evaluate the incidence of PART in the general autopsy population, we looked for histologic evidence of PART in a cohort of 102 autopsy patients coming to the general autopsy service at The University of Vermont Medical Center. Although most studies show PART as a diagnosis of the elderly, living on average a decade longer than patients with AD, our findings suggest support a conclusion that the changes of PART can be present in a much younger population. In addition, our study further suggests a particular prevalence for earlier pathologic tau deposition in women, a finding not described in previous literature.

A total of 102 patients presenting to the general autopsy service at the University of Vermont Medical Center from October of 2018 through December of 2019 were reviewed for neurodegenerative findings including Tau pathology (AT8, Thermo Fisher Scientific, Waltham, MA, USA), amyloid plaques (mOC 64, Abcam, Cambridge, UK), synuclein pathology 12H2L1, Invitrogen, Waltham, MA, USA), and TDP-43 inclusions (EPR5810, Abcam, Cambridge, UK). In 16 autopsies neuropathologic exam identified findings consistent with either Definite PART or Possible PART. Diagnoses were confirmed by two board certified neuropathologists (JD and WP).

Patients with diagnoses of Definite or Possible PART were then sorted by demographic data including gender, age at death, Braak stage, Thal score, and clinical diagnosis of dementia. Cases were also reviewed for other evidence of neurodegenerative processes including TDP43 deposition and hippocampal sclerosis. The data were then further analyzed to reveal any relevant trends. Average age, Braak scores, and Thal scores were compared between males and females by unpaired *t*-test.

The brains of 102 patients examined at time of autopsy were included in this study (age range 26–93 years old). The average age of death for the entire sample of 102 patients was 68.9 years. Sixty males showed a similar average age of death (68.4 years) to the 42 females in the study (69.6 years).

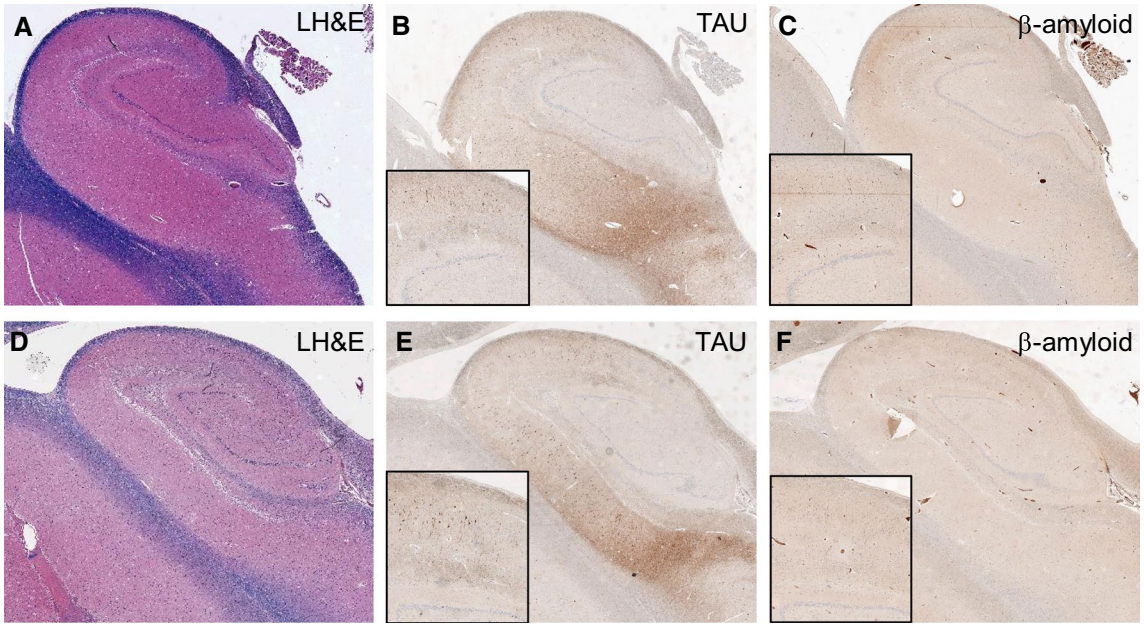

FIGURE 1 Observed PART histopathology. Example of two cases from the 16 case cohort. Panels A through C show Luxol H&E (A), Tau AT8 (B), and β-amyloid (C) stains from the hippocampus of a 64-year-old asymptomatic woman, while panels D through F show Luxol H&E (D), Tau AT8 (E), and β-amyloid (F) stains from the hippocampus of a 74-year-old asymptomatic man. Insets in B, C, E, and F show higher power images of the CA1-CA2 region of the hippocampus. In both cases, a significant burden of neurofibrillary tangles and dystrophic neurites are observed in the hippocampus and entorhinal cortex in the absence of β-amyloid plaques [Colour figure can be viewed at wileyonlinelibrary.com]

Sixteen patients with a significant burden of neurofibrillary tangles, but few if any Ab plaques were diagnosed with either Possible PART or Definite PART (representative histopathology in Figure 1). The 16 identified patients included eight male and eight female subjects with an average age of death of 71.5 years (range 53–90). Zero of the 16 carried any diagnosis of clinical dementia or cognitive impairment prior to death. The overall average age of death of females and males in the study were significantly different at 66.3 and 76.8 years, respectively ($p < 0.05$, Table 1). All subjects were categorized as either Braak stage II or III, with a nonsignificant trend toward a higher Braak score in male patients. Further histopathological review did not find evidence of TDP43-inclusions, synuclein pathology, or hippocampal sclerosis in any of the 16 patients observed for this study.

Eleven of the 16 patients, six female and five male, were diagnosed with Definite PART (Thal stage 0). The average age of death in the Definite PART group was 71.4 years (range 61–90). Consistent with the significant age difference in the entire 16 patient cohort, the average male with Definite PART died at 76.8 years old, while 67.0 years old was the average age of death for Definite PART females (Table 2).

Five of the 16 patients in the study were diagnosed with Possible PART (Thal stage 1–2) and showed an overall average age of death of 71.6 years (range 53–79). Again consistent with the overall cohort, males with Possible PART in this study had an average age of death of 76.7 years, while females in the same group died at the age of 64.0 years on average (Table 3).

TABLE 1 PART patient demographics

Age at death (years)		Braak stage		Thal stage	
Male	**Female**	**Male**	**Female**	**Male**	**Female**
61	53	II	II	0	1
72	61	II	II	1	0
74	63	III	II	0	0
77	64	III	II	0	0
79	67	III	II	1	0
79	70	III	III	2	0
82	75	II	II	0	1
90	77	II	II	0	0
Avg = 76.8*	Avg = 66.3*				

*$p < 0.05$

TABLE 2 Patients with definite PART

Age at death (years)		Braak stage		Thal stage	
Male	**Female**	**Male**	**Female**	**Male**	**Female**
61	61	II	II	0	0
74	63	III	II	0	0
77	64	III	II	0	0
82	67	II	II	0	0
90	70	II	III	0	0
	77		II		0
Avg = 76.8	Avg = 67.0				

TABLE 3 Patients with potential PART

Age at death (years)		Braak stage		Thal stage	
Male	**Female**	**Male**	**Female**	**Male**	**Female**
72	53	II	II	1	1
79	75	III	II	1	1
79		III		2	
Avg = 76.7	Avg = 64.0				

Comparing our small case series to the existing literature, we have identified several areas of concordance in findings related to PART. For one, our case series had a 50/50 distribution of males and females, consistent with the gender distribution described in literature (2). We found no significant association with Braak score and gender, age, or PART status. Furthermore, none of the patients in our study carried a diagnosis of clinical dementia or cognitive decline, consistent with milder clinical course described in the literature. Finally, neurohistopathologic findings in our patients were consistent with the hypothesis that PART is often Braak stage <IV (1,3).

Our data stand out when comparing the average age of death in patients with PART compared to the existing literature (2,10) and the prevailing understanding that PART is a diagnosis of the elderly. The overall average age of death, age of death in Definite PART, and age of death in Possible PART all fall within the eighth decade of life in the current study, roughly 10 years earlier than what has been largely published. These findings support the conclusion that the histologic findings of PART can be present in a much younger population. The results of the present study agree with, and support the conclusions of Braak et al (2011) who have shown that the deposition of pathologic tau can happen throughout life (5), a point often neglected in much of the current literature on PART. Most striking in the current study is the average ages of death at diagnosis among the females; overall average age of death (66 years), Definite PART age of death (67 years), and Possible PART age of death (64 years). The female subjects in our study averaged an age of death some 20–30 years earlier than what has been described in PART research and an average of 11 years earlier than the males in our study across all three categories of subjects (overall, Definite PART, Possible PART). In order to control for possible selection bias (i.e., the average age of our cohort is significantly lower than would be expected in the general autopsy population), we examined the age of death of all patients presenting to our autopsy service over the past 5 years (2015 to 2019) and after excluding all patients under 40 years of age (as in our cohort) we found an average age of death of 68.4 years, 1 year younger than the average age of death for our 101 patient cohort (69.4 years). Therefore, we conclude that our cohort is well representative of the general autopsy population. On the contrary, the utilization of neurodegenerative disease brain banks in previous reports may falsely skew to an older age group coming to autopsy because of a selection bias toward an ethnically nondiverse and higher socioeconomic status of cohort participants (6), especially those that serve as cognitively intact controls, a group comprising a large proportions of those diagnosed at autopsy with PART. Interestingly, two recent studies of Creutzfeldt–Jakob disease with concurrent tau pathology found PART to be a common co-occurring pathology, with an average age of death of 71 and 68 years in the two cohorts (4,11).

Limitations of our study include a small sample size (16 Definite or Possible PART patients out of a 102 patient cohort) consisting of mostly older adults (average age 68.9 years), a small time period of data gathering (14 months), and a patient population limited to the University of Vermont Medical Center which demographically tends have a higher population of Caucasians and northern Europeans than the general population. Those limitations aside, we feel there is strong validity to our findings, and cite in particular the evenly gender-matched subjects, as well as the consistency in trends identified across all three categories of subjects (overall, Definite PART, Possible PART). Furthermore, the average age of males and females in the overall 102 patient study population were almost identical, suggesting the age differences observed in the 16 patient PART cohort are not simply because of selection bias.

Another important consideration is whether the findings observed in this study truly represent PART, or are in fact identifying patients that will go on to develop significant Ab plaque burden, and a diagnosis of Alzheimer disease later in life. Recent genetic studies have shown an association between PART and the microtubule-associated protein tau (*MAPT*) H1 haplotype (8), while no association exists for PART and the APOE ε4 allele, the strongest risk factor for development of AD (10). Genetic studies in such cohorts as presented here will be important in helping to delineate what pathologic findings may truly represent an early presentation of PART, versus the early pathologic changes of Alzheimer disease.

In conclusion, our data support many of the previous efforts to characterize the new entity known as Primary age-related tauopathy (PART). However, our data also suggest that the pathological processes leading to PART can begin decades earlier than what has been published in the literature and are consistent with what has been postulated regarding the tauopathy in sporadic Alzheimer's disease (5). Further study will be crucial to illuminate the role of PART in clinical cognitive decline as well as clinical neuropathology. We recommend considering this diagnosis in patients, particularly females, with normal cognition to mild impairment beginning as early as the sixth decade of life.

KEYWORDS
PART, dementia, neurodegenerative, Tau, Alzheimer

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

WOH, Data analysis and manuscript composition. REM: Data compilation. WWP: Histologic diagnosis. JCD: Histologic diagnosis, manuscript editing, figure composition.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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William O. Humphrey
Rachel Martindale
William W. Pendlebury
John C. DeWitt

Department of Pathology and Laboratory Medicine, The University of Vermont Medical Center, Burlington, VT, USA

Correspondence
John C. DeWitt, Department of Pathology and Laboratory Medicine, MP1-104, The University of Vermont Medical Center, 111 Colchester Ave, Burlington, VT 05401, USA.
Email: John.dewitt@uvmhealth.org

ORCID

John C. DeWitt https://orcid.org/0000-0002-0343-2656

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