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ORIGINAL ARTICLE

Asymmetry of Hippocampal Tau Pathology in Primary Age-Related Tauopathy and Alzheimer Disease

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Abstract

Primary age-related tauopathy (PART) is a neurodegenerative entity defined as neurofibrillary degeneration generally restricted to the medial temporal region (Braak stage I–IV) with complete or near absence of diffuse and neuritic plaques. Symptoms range in severity but are generally milder and later in onset than in Alzheimer disease (AD). Recently, an early predilection for neurofibrillary degeneration in the hippocampal CA2 subregion has been demonstrated in PART, whereas AD neuropathologic change (ADNC) typically displays relative sparing of CA2 until later stages. In this study, we utilized a semiquantitative scoring system to evaluate asymmetry of neurofibrillary degeneration between left and right hippocampi in 67 PART cases and 17 ADNC cases. 49% of PART cases demonstrated asymmetric findings in at least one hippocampal subregion, and 79% of the asymmetric cases displayed some degree of CA2 asymmetry. Additionally, 19% of cases revealed a difference in Braak score between the right and left hippocampi. There was a significant difference in CA2 neurofibrillary degeneration ($p = 0.0006$) and CA2/CA1 ratio ($p < 0.0001$) when comparing the contralateral sides, but neither right nor left was more consistently affected. These data show the importance of analyzing bilateral hippocampi in the diagnostic evaluation of PART and potentially of other neurodegenerative diseases.

Key Words: Alzheimer disease, Braak, CA1, CA2, Neurofibrillary tangles, Primary age-related tauopathy, Thal.

INTRODUCTION

Primary age-related tauopathy (PART) is a relatively recently defined neurodegenerative entity, previously referred to as "tangle-only dementia," "tangle-predominant senile dementia," or simply "age-related neurofibrillary degeneration" (1, 2). It has several features in common with Alzheimer disease (AD) including the presence of tau-positive neurofibrillary tangles (NFTs), consisting of paired helical filaments composed of both 3R- and 4R-tau (3, 4). It is unclear if these NFTs progress through the medial temporal lobe in the same sequence as AD neuropathologic change (ADNC), although they have been shown to have a more limited distribution in PART (3, 5–7). PART NFT pathology progresses in an amyloid-independent manner that is in contrast to ADNC and occurs in a somewhat different spatial arrangement than other amyloid-independent tauopathies (8, 9). Although there currently exists debate as to whether PART is a separate entity or should be included as a subset of ADNC (10–12), PART is currently defined as the presence of NFTs with Braak stages I–IV, Thal phase 0–2, and sparse or absent neuritic plaques by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria (3, 5, 13, 14).

More recently, it has been shown that PART also has different genetic risk factors than those for AD, including a statistical association with the *MAPT* H1 haplotype and lack of association with *APOE* ε4 (15). Further studies have shown that there are morphological differences between PART and ADNC; for example, PART NFTs seem to have a predilection

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for CA2 with less severe CA1 and entorhinal cortex tau pathology (16–21) in contrast to ADNC, which typically spares the CA2/3 regions until later in the disease course (16, 22, 23). In addition, NFTs rarely progress to neocortical stages (Braak V or VI) in the absence of β-amyloid plaques that are characteristic of AD (9), and PART cases frequently lack evidence of both β-amyloid plaques and soluble β-amyloid (15).

Clinically, PART cohorts tend to include a higher percentage of female patients and the "oldest old," and PART cases demonstrate significantly less severe cognitive decline compared with patients with ADNC, although individuals along the full spectrum of cognitive function including normal cognition, mild cognitive impairment, and dementia are typically found in these cohorts (3, 19, 24). As in ADNC, severe tau pathology in PART is more likely to be associated with more severe clinical symptoms (3, 25), although large-scale studies of patients with PART suggest that the CA2 NFT pathology is more related to patient age, and Braak stages in these patients correlate poorly with cognitive decline (measured by Mini-Mental State Examination [MMSE] and Clinical Dementia Rating [CDR]), which suggests that the CA2 pathology may be more a function of aging than a clinical disease process, or perhaps a specific clinical correlate of CA2 involvement is yet to be identified (21). PART has also recently been linked to clinical depression, although it is unclear if depression early in life is a risk factor for PART or if PART pathology may result in depressive symptoms (26).

While many medical centers perform only unilateral evaluation of hippocampi in the diagnosis and workup of neurodegenerative diseases, a certain degree of asymmetry between right and left neocortical and hippocampal pathology in AD (particularly in early Braak stages) has been reported in several studies over the decades (27–30), and more recently in other neurodegenerative diseases including argyrophilic grain disease (AGD) and frontotemporal lobe degeneration (FTLD) (31–35). Review of these cases suggests that tau asymmetry may be more common in cases with low β-amyloid (low Thal phase and CERAD plaque score) (32), suggesting that asymmetry may be more pronounced in PART cases. Herein, we examine the bilateral hippocampi of 67 PART cases and 17 ADNC cases to evaluate the degree of hippocampal NFT asymmetry using a semiquantitative scoring system in each subregion of the bilateral hippocampi (entorhinal cortex, dentate gyrus, and CA1–CA4) (21).

MATERIALS AND METHODS

Case Selection

Cases from State University of New York (SUNY) Upstate Medical University, Syracuse, NY and Mayo Clinic Tissue Registry, Rochester, MN from 2011 to 2019 were reviewed by 2 board-certified neuropathologists (J.M.W. and T.E.R.) blinded to any previous neurologic diagnoses for evidence of phospho-tau, β-amyloid, α-synuclein, and TDP-43. In total, we identified 67 cases of definite or possible PART (defined as Braak stage I–IV, Thal phase 0–2, and absent or sparse neuritic plaques by CERAD criteria) with bilateral hippocampal sampling at hippocampal level 7 (36), irrespective of available clinical information. This included 35 cases of definite PART (Braak I–IV, Thal 0, CERAD 0) and 32 cases of possible PART (Braak I–IV, Thal 1–2, CERAD 0–1) (Table 1) (3). The PART cases included here had a mean age of 79.6 ± 6.1 years old (range 70–94 years). We identified an additional 17 bilateral ADNC cases with a mean age of 75.3 ± 7.5 years old (range 65–91 years). The study was granted an Institutional Review Board exemption from the Institutional Privacy Office at SUNY Upstate Medical University and was certified by HIPAA review.

Immunohistochemistry

Four-μm-thick sections of formalin-fixed, paraffin-embedded tissue underwent heat-induced epitope retrieval using CC1 (Ventana, Tucson, AZ), followed by Bielschowsky Silver Stain (Abcam, Cambridge, United Kingdom) on hippocampal, frontal, and neocortical sections; phospho-tau (p-tau) (AT8; Thermo Fisher Scientific, Waltham, MA) on hippocampal and neocortical sections; β-amyloid (Covance, Inc., Princeton, NJ) on hippocampal, neocortical, cerebellar, and midbrain sections, α-synuclein (Santa Cruz Biotechnology, Santa Cruz, CA) on hippocampal, neocortical, cingulate, midbrain, and medulla sections; and TDP-43 (Sigma-Aldrich, Inc., St. Louis, MO) on hippocampal, neocortical, and cingulate sections, on a Ventana Benchmark Ultra automated stainer, using Ventana UltraView Universal DAB Detection kits, according to the manufacturer protocols. All cases were stained with the same set of antibodies for consistency.

Other Concurrent Pathologies

TDP-43 and α-synuclein were performed on every hippocampal section to evaluate for concurrent limbic-predominant age-related TDP-43 encephalopathy (LATE) or Lewy body disease (LBD) affecting CA1 or CA2 pathology. The cases were also evaluated for evidence of chronic traumatic encephalopathy (CTE) to exclude additional p-tau pathology in the hippocampi.

The pathologic diagnoses included "pure" PART in 45 cases (one of which had a pituitary adenoma and one had metastatic lung adenocarcinoma in the left cerebellum), 8 had large or multifocal ischemic or hemorrhagic infarcts, and 15 had other concurrent neurodegenerative diseases: 4 brainstem-predominant LBD, 4 AGD, 3 age-related p-tau astrogliopathy (ARTAG), 1 possible CTE, 1 multiple system atrophy, and 1 TDP-43-positive frontotemporal dementia/amyotrophic lateral sclerosis (FTLD-TDP-43/ALS).

The ADNC cohort included 5 cases with "pure" AD pathology and 12 cases with additional pathologies, including 3 instances of diffuse neocortical stage Lewy body disease, 1 instance of brainstem-predominant Lewy body disease, 6 cases with ischemic or hemorrhagic insults, 1 case with hippocampal sclerosis, 1 case with evidence of prior trauma, and 3 cases with tumors including meningioma (2 cases) and pituitary adenoma (1 case).

TABLE 1. Semiquantitative Assessment of Bilateral PART and AD Cases

Case #	Entorhinal Tau		CA1 Tau		CA2 Tau		CA3 Tau		CA4 Tau		Dentate Tau		CA2/CA1 Ratio		Braak Score		CERAD	Thal	CAA	Diagnosis
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R				
1	**2**	***1***	**2**	***0.5***	**2**	***0***	0.5	0	0	0	0	0	1	0	**III**	***I***	0	0	0	PART
2	***1***	**2**	1	1	**2**	***1***	0	0.5	0	0.5	0	0	2	1	III	III	0	0	0	PART
3	**2**	***1***	**2**	***1***	**2**	***0***	0.5	0	0	0.5	0	0	1	0	**III**	***II***	0	0	0	PART
4	2	2	1	1	**1**	***0***	0	0	0.5	0	0	0	1	0	III	III	0	0	0	PART
5			1	1	***0***	**2**	0.5	0	0.5	0	0	0	0	2	III	III	0	0	0	PART
6	**2**	***1***	**2**	***1***	**3**	***1***	0	0	1	0	0	0	1.5	1	III	III	0	0	0	PART
7	2	2	3	3	***1***	**2**	0	0.5	0.5	1	0	0	0.33	0.67	IV	IV	0	0	0	PART
8	***2***	**3**	**2**	***1***	0.5	0.5	0	0	0	0	0	0	0.25	0.5	IV	IV	0	0	0	PART
9	2	2	2	2	1	1	0	0.5	0	0.5	0	0	0.5	0.5	IV	IV	0	0	0	PART
10	2	2	1	1	3	3	0.5	0.5	1	1	0.5	0.5	3	3	III	III	0	0	0	PART
11	***2***	**3**	3	3	**2**	***1***	0	0.5	1	0.5	0.5	0	0.67	0.33	IV	IV	0	0	0	PART
12	2	2	1	1	0.5	0.5	0	0	0	0.5	0	0	0.5	0.5	III	III	0	0	0	PART
13	1	1	1	1	***1***	**2**	0	0	0.5	0.5	0	0	1	2	III	III	0	0	0	PART
14	1	1	2	2	1	1	0.5	0.5	0	0	0.5	0.5	0.5	0.5	IV	IV	0	0	0	PART
15	2	2	1	1	***2***	**3**	1	1	0.5	1	0	0	2	3	III	III	0	0	0	PART
16	1	1	**2**	***1***	**2**	***0.5***	1	0.5	1	0	0.5	0	1	0.5	**IV**	***III***	0	0	0	PART
17	1	1	0.5	1	***1***	**2**	0	0.5	0	0.5	0.5	0.5	2	2	***II***	**III**	0	0	0	PART
18	2	2	3	3	***2***	**3**	0.5	0.5	0.5	0.5	0	0.5	0.67	1	IV	IV	0	0	0	PART
19	1	0.5	**2**	***0.5***	**2**	***0***	0.5	0	**1**	***0***	0.5	0	1	0	**IV**	***I***	0	0	0	PART
20	***0.5***	**2**	0.5	1	***0***	**1**	0	0.5	0	0.5	0	0.5	0	1	***I***	**III**	0	0	0	PART
21	**2**	***1***	1	0.5	**2**	***0.5***	0	0	**1**	***0***	0	0	2	1	**III**	***II***	0	0	0	PART
22	1	1	0.5	0.5	2	2	0.5	0.5	0	0	0	0	4	4	II	II	0	0	0	PART
23	1	1	1	1	1	1	0.5	0.5	0	0	0	0	1	1	II	II	0	0	0	PART
24	1	1	0.5	0.5	***0***	**2**	0.5	0	0	0	0	0	0	4	II	II	0	0	0	PART
25	2	2	1	1	0	0	0	0.5	0	0.5	0	0	0	0	II	II	0	0	0	PART
26	2	2	1	1	0.5	0	0.5	0.5	0	0	0.5	0	0.5	0	II	II	0	0	0	PART
27	1	0.5	1	0.5	0.5	0.5	0	0	0.5	0	0	0	0.5	1	I	I	0	0	0	PART
28	0.5	0.5	0.5	0.5	1	0.5	0	0	0.5	0	0	0	2	1	I	I	0	0	0	PART
29	0.5	0.5	0.5	0.5	0.5	1	0.5	0	0.5	0.5	0.5	0	1	2	I	I	0	0	0	PART
30	0.5	0.5	0.5	0.5	0.5	0	0	0	0	0	0	0	1	0	I	I	0	0	0	PART
31	0.5	0.5	1	0.5	0.5	0	0	0	0.5	0	0	0	0.5	0	I	I	0	0	0	PART
32	1	0.5	0.5	0.5	0	0	0	0	0	0	0	0	0	0	I	I	0	0	0	PART
33	0.5	0.5	0	0.5	0	0	0	0	0	0.5	0	0	0	0	I	I	0	0	0	PART
34	0.5	0.5	0	0	0.5	0	0	0	0	0	0	0	0	0	I	I	0	0	0	PART
35	0.5	1	0.5	0.5	0.5	0.5	0	0	0.5	0	0	0	1	1	I	I	0	0	0	PART
36	2	2	2	2	***1***	**3**	0.5	0.5	0.5	0	0	0	0.5	1.5	IV	IV	0	1	0	PART
37	2	2	2	2	1	1	0	0.5	0	0	0	0	0.5	0.5	IV	IV	0	1	0	PART
38	2	2	2	2	***1***	**2**	0.5	0	0.5	0	0	0	0.5	1	IV	IV	0	1	0	PART
39	2	2	2	2	1	1	0.5	0	0	0	0	0	0.5	0.5	IV	IV	0	1	0	PART
40	1	1	***0.5***	**2**	***0***	**2**	0	0.5	0	0	0	0	0	1	***II***	**III**	0	1	0	PART

(continued)

TABLE 1. Continued

Case #	Entorhinal Tau		CA1 Tau		CA2 Tau		CA3 Tau		CA4 Tau		Dentate Tau		CA2/CA1 Ratio		Braak Score		CERAD	Thal	CAA	Diagnosis
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R				
41	2	2	3	3	2	2	0.5	0.5	0.5	0.5	0	0.5	0.67	0.67	IV	IV	0	1	0	PART
42	1	1	2	2	2	2	1	1	0	0	0	0.5	1	1	IV	IV	0	2	0	PART
43	1	1	2	2	3	3	0.5	1	1	1	0.5	0.5	1.5	1.5	IV	IV	0	1	0	PART
44	**2**	***1***	**2**	***0.5***	0	0	0	0	0	0	0	0	0	0	**III**	***II***	0	2	1	PART
45	**2**	***1***	1	1	***2***	**3**	0.5	0.5	***0.5***	**3**	0	0	2	3	III	III	0	2	0	PART
46	***1***	**2**	**3**	***2***	2	2	1	0.5	1	0.5	1	1	0.67	1	III	III	0	2	0	PART
47	***1***	**2**	0.5	1	0.5	1	0	0	0	0.5	0	0	1	1	***II***	**III**	0	2	0	PART
48	1	0.5	***1***	**2**	3	3	***0.5***	**2**	***1***	**3**	***0.5***	**2**	3	1.5	III	III	0	2	0	PART
49	1	1	1	1	***1***	**2**	0	0.5	0.5	0	0	0.5	1	2	III	III	0	1	0	PART
50	0.5	0.5	1	0.5	**2**	***1***	0	0	0.5	0	0	0	2	2	II	II	0	1	0	PART
51	0.5	0.5	0.5	1	***0***	**2**	0	0	0	0	0	0	0	2	***I***	**II**	0	1	0	PART
52	1	1	1	1	0.5	0.5	0	0	0	0	0	0	0.5	0.5	III	III	0	1	0	PART
53	0.5	0.5	0.5	0.5	0	0	0	0	0	0	0	0	0	0	I	I	0	1	1	PART
54	1	1	0.5	0.5	**1**	***0***	0	0	0.5	0	0.5	0	2	0	II	II	0	2	0	PART
55	3	3	2	2	2	2	0.5	0.5	1	0.5	0	0	1	1	IV	IV	1	1	1	PART
56	3	3	***1***	**2**	2	2	0.5	0	1	0.5	0	0	2	1	IV	IV	1	1	0	PART
57	2	2	2	2	3	3	0.5	0.5	0.5	0.5	0.5	0.5	1.5	1.5	IV	IV	1	2	1	PART
58	2	2	2	2	3	3	0.5	0.5	0.5	0.5	0	0.5	1.5	1.5	IV	IV	1	1	1	PART
59	1	1	1	1	2	2	0	0	0	0	0	0	2	2	III	III	1	2	0	PART
60	2	2	2	2	3	3	1	0.5	0.5	0.5	0.5	1	1.5	1.5	IV	IV	1	1	0	PART
61	3	3	2	2	3	3	0	0.5	1	0.5	0.5	0.5	1.5	1.5	IV	IV	1	1	1	PART
62	**2**	***1***	1	0.5	0.5	0.5	0	0	0.5	0	0	0.5	0.5	1	**III**	***II***	0	2	0	PART
63	1	1	2	2	3	3	0.5	0.5	1	0.5	0.5	0.5	1.5	1.5	III	III	1	2	1	PART
64	1	1	1	1	1	0.5	0	0	0	0	0	0	1	0.5	II	II	1	1	0	PART
65	1	0.5	1	0.5	**2**	***1***	0.5	0	0.5	0.5	0	0	2	2	**II**	***I***	1	1	0	PART
66	1	0.5	0.5	0.5	0.5	1	0	0	0	0	0	0	1	2	I	I	1	1	0	PART
67	0.5	0.5	0	0	0.5	0	0	0	0	0	0	0	0	0	I	I	0	2	0	PART
68	3	3	3	3	1	1	1	0.5	**2**	***1***	**2**	***1***	0.33	0.33	VI	VI	3	5	0	ADNC
69	3	3	2	2	2	2	0.5	0	1	0.5	0	0	1	1	V	V	2	4	1	ADNC
70	3	3	3	3	0.5	1	1	0.5	1	1	0.5	1	0.17	0.33	V	V	3	4	1	ADNC
71	3	3	3	3	***1***	**2**	0.5	1	1	1	1	1	0.33	0.67	VI	VI	3	5	0	ADNC
72	3	3	3	3	0.5	1	0.5	1	1	1	0.5	0.5	0.17	0.33	V	V	2	4	0	ADNC
73	3	3	3	3	1	0.5	0.5	0.5	1	1	1	1	0.33	0.17	VI	VI	3	5	1	ADNC
73	3	3	3	3	2	2	1	1	1	1	1	1	0.67	0.17	VI	VI	2	5	0	ADNC
74	***2***	**3**	3	3	1	1	1	1	0.5	1	1	1	0.33	0.33	V	V	3	5	1	ADNC
75	3	3	3	3	1	1	0.5	1	0.5	0.5	2	2	0.33	0.33	VI	VI	3	5	1	ADNC
76	3	3	3	3	1	1	1	1	1	1	1	1	0.33	0.33	VI	VI	3	4	0	ADNC
77	3	3	3	3	1	1	0.5	1	1	1	0.5	0.5	0.33	0.33	V	V	3	5	0	ADNC
78	3	3	3	3	2	2	0.5	1	1	0.5	0.5	0.5	0.67	0.67	IV	IV	2	4	0	ADNC
79	2	2	2	2	2	2	0.5	0.5	0	0.5	0	0	1	1	V	V	1	3	0	ADNC

(continued)

TABLE 1. Continued

Case #	Entorhinal Tau		CA1 Tau		CA2 Tau		CA3 Tau		CA4 Tau		Dentate Tau		CA2/CA1 Ratio		Braak Score		CERAD	Thal	CAA	Diagnosis
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R				
80	*1*	3	3	3	2	2	1	1	2	2	0.5	1	0.67	0.67	IV	IV	3	4	0	ADNC
81	*2*	3	3	3	2	2	0.5	0.5	1	0.5	0.5	0.5	0.67	0.67	V	V	3	4	0	ADNC
82	*1*	2	0.5	0.5	***0***	1	0	0.5	0	0	0	0	0	2	***II***	III	1	3	0	ADNC
83	0.5	0.5	3	3	3	3	0.5	0.5	1	1	1	1	1	1	IV	IV	2	3	1	ADNC

Note: Underlined = ≥1 semiquantitative score/Braak score greater than the contralateral counterpart; italic = ≤1 semiquantitative score/Braak score greater than the contralateral counterpart.

Semiquantitative Scoring

In all cases, bilateral hippocampal regions (entorhinal cortex, CA1, CA2, CA3, CA4, and dentate gyrus) were individually examined by J.M.W. and T.E.R. for density of NFTs and p-tau-positive dystrophic neurites with Bielschowsky silver stains and p-tau immunohistochemical stains. Braak stage, CERAD score, and Thal phase were also evaluated bilaterally according to previously established criteria (5, 14, 37). A score of 0.5 was given for single or "rare" tangles, 1 for "mild" p-tau pathology, 2 for "moderate" p-tau pathology, and 3 for "severe" p-tau pathology (Supplementary Data Fig. S1) (21). Overall differences in tau burden between sides (labeled as "higher tau burden" and "lower tau burden") were determined by summing the semiquantitative tau scores for each region evaluated on each side. The CA2/CA1 ratio was calculated for each side in each case evaluated.

Statistical Analysis

Differences in mean p-tau burden in hippocampal subregions were calculated using Analysis of Variance (ANOVA) (21), and differences between subregions in PART and ADNC were calculated using the Mann-Whitney *U* test (17). Proportion of cases in each group with asymmetry was calculated using the Fisher exact test. All statistical calculations were performed with GraphPad Prism version 8.4 (GraphPad, La Jolla, CA).

RESULTS

Comparison of PART and ADNC

CA2 pathology severity was equal to or greater than CA1 pathology in 63% of PART hippocampi examined, but only 18% of ADNC hippocampi displayed this pattern (Table 1). There was significantly less neurofibrillary degeneration identified in the entorhinal region, CA1, CA3, CA4, and dentate gyrus in the PART cases compared with ADNC cases ($p < 0.0001$), but CA2 pathology in PART cases was statistically equivalent to CA2 pathology in ADNC cases ($p = 0.4705$) (Fig. 1A). The average semiquantitative CA2 tau-positive neurofibrillary pathology in the PART cohort was statistically equal to the pathology in CA1, and there was relatively less p-tau staining in the entorhinal cortex. This is in contrast to ADNC, in which there is relative CA2–CA4 sparing and more severe p-tau pathology in CA1 and the entorhinal cortex. There was a significant difference in CA2/CA1 ratios between PART and ADNC in both overall hippocampi ($p = 0.0003$), similar to previous reports (16, 17, 21), and in the sides with more significant overall p-tau burden ($p = 0.002$) (Fig. 1B).

Asymmetry in the PART Cohort

We evaluated bilateral hippocampi in both PART and ADNC cases. Within the PART cohort, 49% of cases (33/67) displayed asymmetry in at least one hippocampal subregion (defined as a difference of at least one by semiquantitative analysis), and 19% of cases (13/67) revealed asymmetry in Braak stage between left and right hippocampi (Table 2).

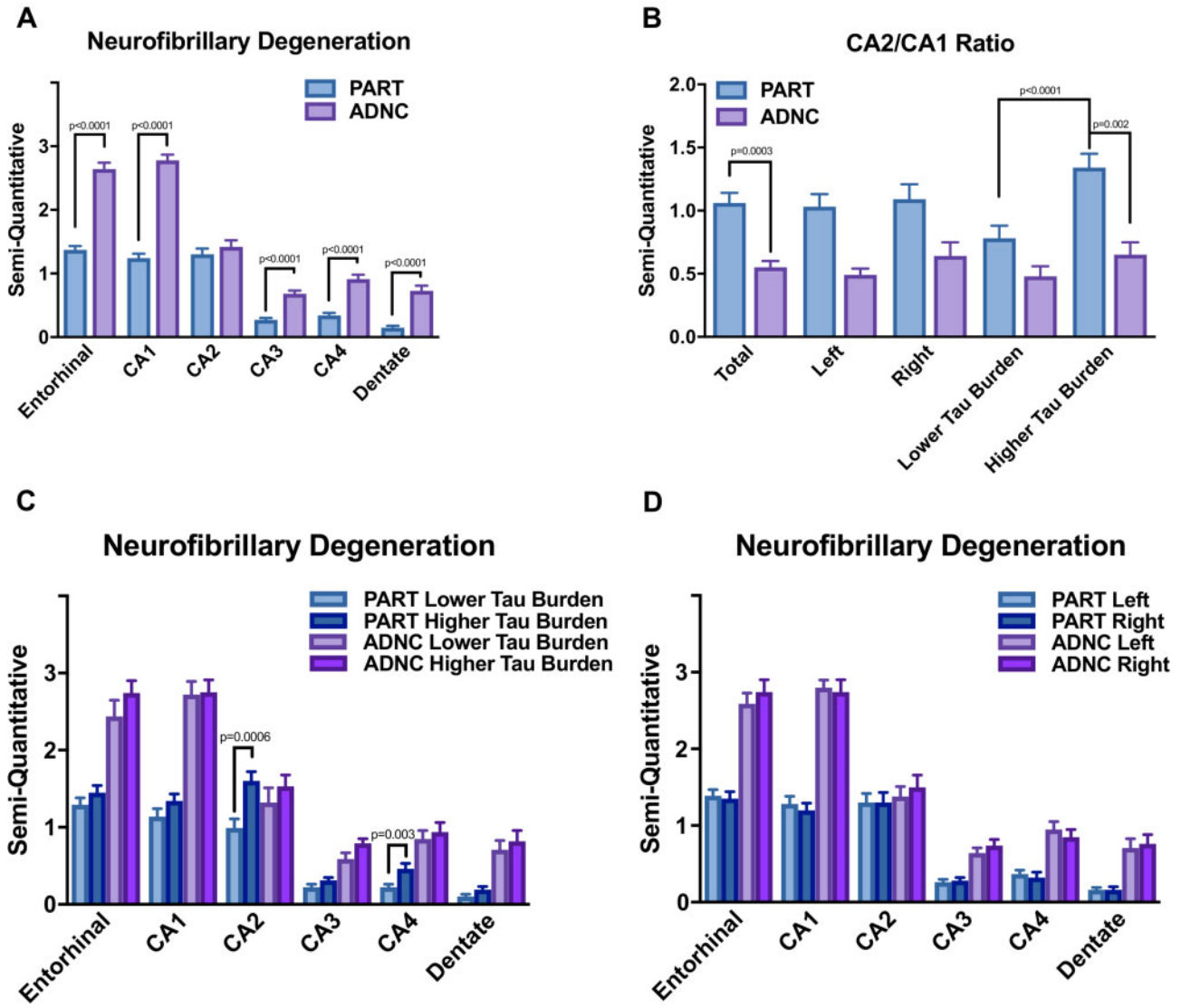

FIGURE 1. Bar graphs demonstrating a significantly higher level of p-tau-positive neurofibrillary degeneration between ADNC and PART in the entorhinal, CA1, CA3, and CA4 regions of the hippocampi ($p < 0.0001$ in all cases), but no significant difference was found between ADNC and PART in overall CA2 p-tau burden ($p = 0.4705$) **(A)**. There is a significant difference in total CA2/CA1 ratio between total PART and ADNC cases ($p = 0.0003$), between the PART and ADNC cases on the side with the more severe p-tau burden ($p = 0.002$), and between the sides with less and more severe p-tau burden within the PART group ($p < 0.0001$) **(B)**. There was a significant difference in p-tau pathology only in the CA2 region ($p = 0.0006$) and CA4 region ($p = 0.0034$) of PART cases between the sides with more and less severe p-tau pathology **(C)**, however, there is no significant difference in p-tau-positive neurofibrillary degeneration between right and left sides in any region in either disease process **(D).**

The asymmetry occurred most frequently and was most severe in the CA2 subregion of the hippocampus (Fig. 2; Supplementary Data Fig. S2). There was a significant difference in CA2/CA1 ratio in hippocampal sides with greater p-tau burden compared with hippocampal sides with less p-tau burden ($p < 0.0001$) (Fig. 1B) and a significant difference in p-tau-positive pathology in the CA2 ($p = 0.0006$) and CA4 ($p = 0.0034$) regions of PART cases between the side with greatest and least p-tau burden (Fig. 1C), but no quantifiable asymmetry was consistently seen between left and right side in PART or ADNC in any hippocampal region (Fig. 1D). Asymmetry of β-amyloid was not seen in the PART cases, although this is likely due in part to the infrequency of diffuse or neuritic plaques in these cases.

There was a trend toward a greater percentage of PART cases with asymmetry in at least one subregion (49%) compared with the ADNC group (35%), and a trend toward a greater percentage of PART cases with asymmetrical Braak stages (19%) compared with the ADNC group (6%). ADNC cases were more frequently asymmetrical in the entorhinal region, while the majority of PART cases with asymmetry had asymmetrical findings in the CA2 subregion (79% of the PART cases with asymmetry) (Table 1).

TABLE 2. Overview of PART and ADNC Asymmetry

Diagnosis	n	Mean Age; Range (Years)	Total Asymmetric Cases	Total Asymmetric Hippocampal Regions	Cases With Asymmetric Braak Scores	Hippocampal Regions With Asymmetry					
						Entorhinal	CA1	CA2	CA3	CA4	Dentate
PART	67	79.6; 70–94	49.3% (33/67)	14.0% (56/401)	19.4% (13/67)	19.7% (13/66)	16.4% (11/67)	38.8% (26/67)	1.5% (1/67)	6.0% (4/67)	1.5% (1/67)
ADNC	17	75.3; 65–91	35.3% (6/17)	7.8% (8/102)	5.9% (1/17)	23.5% (4/17)	0%	11.8% (2/17)	0%	5.9% (1/17)	5.9% (1/17)

These findings highlight significant asymmetry in tau-positive NFT pathology in PART cases, primarily in the CA2 subregion, that does not depend on a specific laterality, and this asymmetry was not observed as frequently in cases with ADNC.

DISCUSSION

This is the first study to evaluate a cohort of PART cases for hippocampal asymmetry, although asymmetrical pathology in the hippocampus and neocortex has been investigated in other neurodegenerative diseases, with varying clinical implications (27–29, 31–35). Similar to previous studies (16, 17, 21), we demonstrate that the average level of CA2 pathology is statistically indistinguishable in PART compared with ADNC, while the NFT pathology in entorhinal, CA1, CA3, CA4, and dentate gyrus is significantly lower in PART compared with ADNC (Fig. 1A), and the CA2/CA1 ratio is significantly higher in PART compared with ADNC (Fig. 1B). In addition, we demonstrate that the CA2/CA1 ratio is significantly higher in the side with higher overall p-tau pathology burden in PART cases but not ADNC cases (Fig. 1B), and the overall level of CA2 and CA4 pathology is higher in the side with increased overall p-tau pathology in PART, but not in any other CA subregion in PART or ADNC (Fig. 1C). This difference is not consistently associated with either side (Fig. 1D). Asymmetry in at least one hippocampal subregion of at least one degree by our semiquantitative score system was identified in 33/67 PART cases (49%), and 13/67 PART cases displayed asymmetry in Braak stage (19%), compared with ADNC, in which 35% of cases (6 of 17 asymmetric cases) demonstrated asymmetry in at least one hippocampal subregion, and 6% (1/17) displayed asymmetrical Braak stages. The ADNC case with asymmetrical Braak stages had low p-tau burden bilaterally, similar to previous observations (23).

Given the propensity for Lewy body disease to preferentially affect the CA2 subregion (38, 39) and LATE pathology to affect the CA1/subiculum (40–42), each case was screened for these disorders with additional stains for α-synuclein and TDP-43 to rule out these potential confounding factors. The PART cohort included no cases with either additional diagnosis, although there were 4 cases with brainstem predominant Lewy body disease. The ADNC cohort had multiple instances of concurrent limbic/neocortical Lewy body disease and hippocampal sclerosis, and those had no significant increase in CA2 p-tau pathology compared with other cases. One case of possible CTE was also identified among the 67 PART cases.

PART as a disease entity is generally believed to display milder symptoms on average than AD, corresponding to the more limited Braak stage (3), although there are cases with severe memory deficits and dementia, especially in older patients in these cohorts, and has been associated with depression (26). The CA2 hippocampal subfield receives projections primarily from the entorhinal cortex and projects to the ventral CA1 neurons, as well as forming a reciprocal circuit with the lateral and medial septum, circuitry thought to be involved with social cognition (43) including encoding names and faces (44). In addition, animal models have hinted at roles for CA2 in social memory (45–47). However, in disorders such as LBD

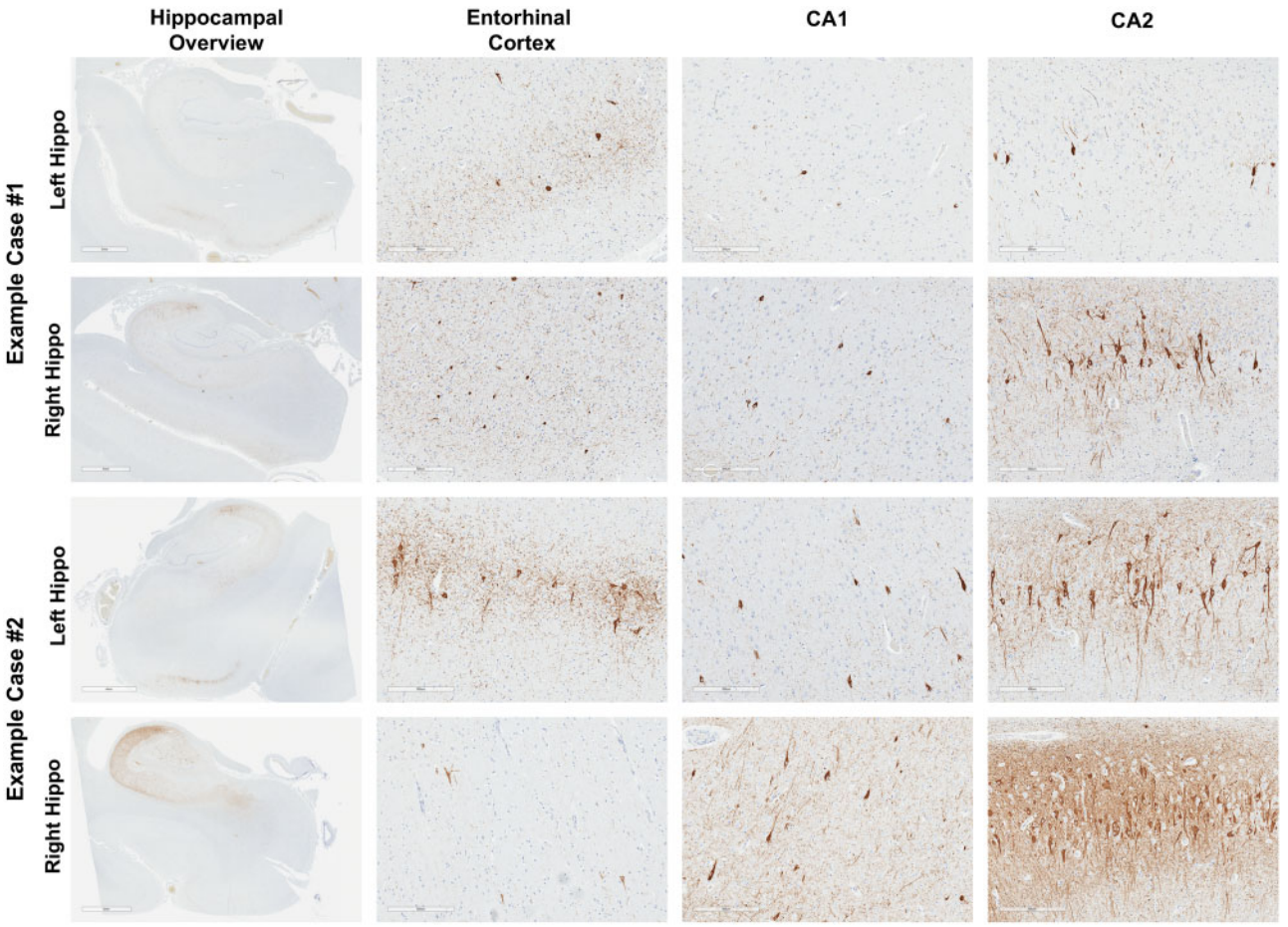

FIGURE 2. p-Tau (AT8) staining of bilateral hippocampi from 2 representative cases of PART, with hippocampal overview and higher magnification of entorhinal cortex, CA1, and CA2 hippocampal, demonstrating variable asymmetry in CA2 (example case #1) and entorhinal cortex, CA1, and CA2 (example case #2). Scale bars for hippocampal overview panels = 4 mm, all other scale bars = 300 μm.

where CA2 is affected, it has been demonstrated that the degree of pathology in CA1 is more correlated with cognitive decline than the degree of CA2 pathology (48).

AGD is a 4R-tauopathy that, similar to PART, may occur in the absence of β-amyloid, has a predilection for the CA2 subregion, tends to affect older individuals than classic AD, and may result in dementia in the more advanced stages (49–51). Studies have shown histologic asymmetry in the majority of AGD cases, and patients with a greater pathologic burden on the left side had more significant dementia than those with more right-sided pathology, which is hypothesized to be due to more prominent impairment in the dominant hemisphere in these cases (23). Similarly, primary progressive aphasia (PPA), a clinical syndrome that can result from multiple underlying pathologies including ADNC and FTLD, among other entities (34), tends to result in several different variants of language impairments including logopenic and semantic aphasia (52). As with AGD, the symptoms of PPA seem to be related to an asymmetric neurodegeneration in the dominant hemisphere (33–35).

While PART is a purely neuropathologic diagnosis that does not require the presence of any specific clinical features, a limitation of the current study is that the majority of these cases were collected from community cohorts without detailed neurology and neuropsychology data (CDR, MMSE, or other verified dementia history), and so we were unable to correlate the CA2 pathology or CA2 asymmetry in PART cases with any definitive clinical symptoms. Previous work has suggested that the excess CA2 neurofibrillary degeneration burden present in PART cases may be a function of age and may not correlate well with CDR or MMSE results (21). It is possible that the asymmetry found in these cases may serve as a source of cognitive reserve in which the side with lower p-tau pathology may compensate to some degree for the side with greater p-tau pathology, and this may partially explain the lack of correlation between hippocampal pathology and clinical symptoms found in some studies that utilized unilateral hippocampi only. In the future, however, prospective studies to investigate the clinical and pathologic correlations of asymmetry in this disease and to identify any potential symptomatic differences between increased p-tau burden in the dominant and nondominant hemispheres should prove enlightening. Despite the lack of comprehensive clinical information in this set of cases, this study suggests that there are a significant number of

PART cases that display asymmetry, and findings from other related neurodegenerative disease states suggest that asymmetry may indeed be clinically relevant.

The finding that PART is more frequently asymmetric than ADNC, and observations from previous data on cases with Alzheimer-type pathology (23) demonstrating that p-tau pathology appears more asymmetric in cases with lower Thal phase and CERAD scores, suggest that p-tau asymmetry may be more pronounced in cases without β-amyloid or with minimal concurrent β-amyloid deposition. It should be noted, however, that β-amyloid pathology has also been found to be asymmetric in a subset of ADNC cases (23).

Current standard workup for neurodegenerative diseases at most institutions includes only unilateral histologic examination of the hippocampus and neocortex with retention of the opposite hemibrain for nonmorphologic research analyses; this study demonstrates that unilateral examination of some brain regions may mislead the examiner in judging the severity of disease and has potential implications for the staging of PART and ADNC. For more accurate neurolopathogical diagnoses, and a more complete assessment of incidence and severity, a recommendation for bilateral tissue examination is supported by this study. In addition, these findings, along with the more general finding that PART displays an early selective vulnerability of the CA2 hippocampal subfield for neurofibrillary degeneration (16, 17, 21), and molecular studies indicating divergent underlying genetic risk factors (3, 7, 9, 10, 15, 25), support the hypothesis that PART is a neuropathologically distinct entity from AD.

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