Alzheimer's & Dementia 13 (2017) 1048-1053

Short Report

Cognitive decline associated with pathological burden in primary age-related tauopathy

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Abstract

Introduction: Primary age-related tauopathy (PART) is a neuropathological diagnosis characterized by tau neurofibrillary tangles (NFTs) in the absence of amyloid plaque pathology. Although most individuals over 50 years of age have evidence of NFTs, the clinical and cognitive consequences of PART are not known.

Methods: We evaluated 226 neuropathologically confirmed PART cases from the National Alzheimer's Coordinating Center database who participated in a total of 846 longitudinal neuropsychological assessments from the Alzheimer's Disease Center program's Uniform Data Set. Mixed-effects statistical models tested whether cognitive decline was associated with Braak stage NFT burden.

Results: Higher stages of NFT burden in PART, with no evidence or minimal evidence of amyloid pathology, were associated with more rapid decline on tasks involving episodic and semantic memory along with tests of processing speed and attention.

Discussion: We conclude that PART has cognitive consequences that should be considered in the context of emerging tau-targeted therapies in age-associated neurodegenerative diseases.

Keywords: Primary age-related tauopathy; Tau; Cognition; Clinical prognosis

1. Introduction

Alzheimer's disease (AD) is neuropathologically characterized by the presence of both tau neurofibrillary tangles (NFTs) and amyloid β (Aβ) plaques [1]; yet, autopsy studies have identified a subset of individuals who have NFTs in the absence of Aβ. Recently, the term primary age-related tauopathy (PART) was coined to describe this condition [2], defined by neuropathological criteria of the presence of predominately limbic NFT pathology up to Braak stage IV [3]. PART is further defined as "definite" with no evidence of neuritic plaque density or "possible" with minimal evidence of neuritic plaques [2]. However, criteria for the diagnosis of PART are strictly neuropathological, and little is known about the cognitive manifestations associated with PART.

Historically, when associated with dementia, PART was previously termed tangle-predominant senile dementia [4] or senile dementia of the NFT type [5]. However, NFTs in the absence of Aβ pathology are also quite common in cognitively normal elderly individuals [6,7] with most individuals over the age of 50 having some level of tau inclusions [8]. Therefore, because PART can be associated with dementia or normal cognition in aging adults, it is necessary to evaluate the direct influence of NFT burden on cognition in a pathologically, rather than clinically, defined cohort. Although it has been demonstrated that Mini-Mental State Examination (MMSE) is correlated with increased NFT burden in PART [2], more detailed and longitudinal clinical data have not been characterized. This cohort study, therefore, aims to identify the longitudinal cognitive consequences of PART and identify whether

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http://dx.doi.org/10.1016/j.jalz.2017.01.028

cognitive decline is associated with increases in NFT burden in the absence of amyloid pathology.

2. Methods

2.1. Study population

Neuropathological and neuropsychological data were obtained for all individuals over 50 years old at death from the National Alzheimer's Coordinating Center (NACC) database, and we report data from 32 past and present Alzheimer's Disease Centers (ADCs). All participants completed a neuropsychological assessment from the Uniform Data Set (UDS), described in detail elsewhere [9] and summarized in Table 1. We also evaluated the frequency of clinically detected cognitive impairment using a clinician's rating of "impaired" or "cognitively normal" obtained from the UDS.

To define neuropathological groups, we queried Braak stage and neuritic plaque ratings available in the NACC neuropathological database. These ratings are performed using independent methods (e.g., PHF-1, Thioflavin-S, Silver staining) by trained neuropathologists from each participating ADC, but despite heterogeneous methods there is established excellent agreement in ratings across sites [10]. We then selected the subset of individuals with neuropathological evidence of NFTs consistent with Braak stage I/II or III/IV [3]. For each Braak stage group, we classified each individual as having definite (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] = 0) or possible (CERAD = 1) PART using published criteria [2]. To focus exclusively on PART, we excluded individuals who met primary or secondary neuropathological criteria for a related neurodegenerative disease such as frontotemporal degeneration (e.g., tau, ransactive response DNA binding protein 43 kDa [TDP-43], or fused

Table 1
Median (IQR) and frequency summaries of demographics, baseline assessment of neuropsychological performance, and final assessment of neuropsychological performance for 226 individuals with neuropathological confirmation PART

	Visit	Definite PART I/II	Definite PART III/IV	Possible PART I/II	Possible PART III/IV	*P* value
Demographics						
N	—	79	49	39	59	—
Sex, % female	—	48.1%	61.2%	15.9%	64.4%‡	.021
Education, y	—	16.0 (12.5–18.0)	15.0 (14.0–18.0)	16.0 (13.0–18.0)	15.0 (12.0–16.5)	.518
Age at death, y	—	84.0 (78.0–90.0)	92.0* (88.0–94.0)	86.0 (82.0–91.0)	92.0† (86.0–96.0)	<.001
Frequency of visits, quantity	—	3.0 (2.0–5.5)	3.0 (2.0–5.0)	4.0 (3.0–5.0)	3.0 (2.0–5.0)	.733
Cognitively impaired, % total	—	37.7%	53.1%*	50.0%	69.0%†	
Age, y	Baseline	80.0 (73.0–86.0)	87.0* (84.0–90.0)	82.0 (77.5–85.0)	87.0† (81.0–91.5)	<.001
	Final	83.0 (77.0–88.5)	90.0* (87.0–93.0)	84.0 (80.5–89.5)	90.0† (85.0–94.5)	<.001
Global						
MMSE, total correct	Baseline	28.0 (27.0–30.0)	28.0 (26.0–29.0)	29.0 (27.0–29.5)	28.0 (26.5–29.0)	.328
	Final	28.0 (26.5–29.0)	28.0 (25.0–29.0)	28.0 (25.5–30.0)	27.0 (26.0–29.0)	.143
Executive						
Trails-B, completion time	Baseline	105.0 (78.0–150.5)	145.0* (90.0–190.0)	102.0 (82.5–132.0)	131.0 (105.5–184.5)	.003
	Final	123.0 (85.5–233.5)	164.0 (91.0–252.0)	112.0 (85.5–172.5)	199.0†,‡ (138.5–300.0)	.001
Memory						
Logical memory immediate, # words	Baseline	13.0 (9.5–16.0)	12.0 (7.0–16.0)	13.0 (8.0–15.0)	12.0 (10.0–15.0)	.518
	Final	14.0 (10.0–17.0)	12.0 (6.0–15.0)	12.0 (4.0–16.5)	11.0 (7.0–15.0)	.137
Logical memory delayed, # words	Baseline	12.0 (9.5–15.0)	11.0 (7.0–14.0)	11.0 (4.5–14.5)	11.0 (7.0–13.0)	.111
	Final	12.0 (8.0–16.0)	10.0 (1.0–15.0)	11.0 (2.0–16.0)	10.0 (5.0–13.5)	.092
Processing speed/attention						
WAIS Digit Symbol, correct pairs	Baseline	38.0 (29.8–46.0)	36.0 (28.0–43.0)	37.0 (31.8–45.0)	32.0† (24.8–38.3)	.015
	Final	33.0 (26.0–42.0)	31.0 (25.3–42.8)	32.0 (27.0–41.0)	25.0† (20.8–33.0)	.008
Trails-A, completion time	Baseline	41.0 (32.0–48.0)	45.0 (32.0–56.0)	42.0 (32.0–54.0)	45.0 (35.0–58.5)	.312
	Final	47.0 (33.5–61.0)	48.0 (35.0–74.0)	47.0 (35.3–56.8)	63.0† (42.0–78.0)	.043
Digit Span Forward, span length	Baseline	8.0 (7.0–10.5)	8.0 (7.0–9.0)	9.0 (7.0–10.0)	8.0 (7.0–10.0)	.34
	Final	8.00 (7.0–9.0)	8.00 (6.0–9.0)	8.00 (7.0–9.0)	8.00 (7.0–9.0)	.997
Digit Span Backward, span length	Baseline	7.0 (5.0–8.0)	6.0 (4.0–8.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	.103
	Final	6.0 (5.0–8.0)	6.0 (4.0–7.0)	6.0 (5.0–7.0)	5.0 (4.0–7.0)	.161
Language and semantic memory						
Category fluency, # animal words	Baseline	17.0 (13.0–22.0)	17.0 (12.0–22.0)	17.0 (14.5–21.0)	16.0 (13.0–19.5)	.52
	Final	17.0 (11.0–21.0)	15.0 (10.0–20.0)	16.0 (11.5–19.0)	13.0 (10.0–17.0)	.065
Boston Naming Test, total correct	Baseline	28.0 (26.0–29.0)	27.0* (24.0–28.0)	27.0 (24.5–28.0)	25.0† (23.0–28.0)	.004
	Final	28.0 (25.0–29.0)	27.0* (24.0–28.0)	27.0 (22.5–29.0)	26.0 (23.50, 27.0)	.015

Abbreviations: IQR, interquartile range; MMSE, Mini-Mental State Examination; PART, primary age-related tauopathy.
NOTE. Significant post hoc differences (all $P < .05$).
*Definite PART III/IV relative to definite PART I/II.
†Possible PART III/IV relative to possible PART I/II.
‡Possible PART III/IV relative to definite PART III/IV.