Neurobiology of Aging 43 (2016) 101–110

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Braak stage and trajectory of cognitive decline in noncognitively impaired elders

Elliott J. Mufson [a,*], Michael Malek-Ahmadi [b], Noelle Snyder [b], Jake Ausdemore [b], Kewei Chen [b], Sylvia E. Perez [a]

[a] Department of Neurobiology, Barrow Neurological Institute, Phoenix, AZ, USA
[b] Banner Alzheimer's Institute, Phoenix, AZ, USA

ARTICLE INFO

Article history:
Received 8 January 2016
Received in revised form 2 March 2016
Accepted 3 March 2016
Available online 10 March 2016

Keywords:
Aging
Alzheimer's
Dementia
Longitudinal
Neurofibrillary tangles
Cognition

ABSTRACT

In a previous cross-sectional study, we found that nondemented elderly participants from the Rush Religious Orders Study (RROS) displayed a wide range of Braak neurofibrillary tangle and amyloid plaque pathology similar to that seen in prodromal and frank Alzheimer's disease. Here, we examined longitudinal changes in cognitive domains in subjects from this cohort grouped by Braak stage using linear mixed effects models. We found that the trajectory of episodic memory composite (EMC), executive function composite (EFC), and global cognitive composite scores (GCS: average of EMC and EFC scores) was significantly associated with age at visit over time, but not with Braak stage, apolipoprotein E (APOE) ε4 status or plaque pathology alone. By contrast, the combined effects of Braak stage, APOE status, and age at visit were strongly correlated with the trajectory of EMC, EFC and GCS performance over time. These data suggest that age and APOE ε4 status, rather than Alzheimer's disease-related pathology, play a more prominent role in the trajectory of cognitive decline over time in this elderly nondemented population. However, the findings reported require confirmation in a larger cohort of cases.

1. Introduction

Older people without dementia display neurofibrillary tangles (NFTs) and beta amyloid (Aβ) plaques, the two neuropathology hallmarks of Alzheimer's disease (AD) (Bennett et al., 2002; Guillozet et al., 2003; Markesbery, 2010; Morris and Price, 2001; Morris et al., 2001; Mufson et al., 1999, 2016; Price et al., 2009; Tomlinson et al., 1970; Wilson et al., 2006). However, there are relatively few prospective studies on the association between premortem cognitive function and AD pathology in people who died with a clinical diagnosis of no cognitive impairment (NCI) but display extensive NFT deposition within the medial temporal lobe (MTL) memory circuit. The Braaks (Braak and Braak, 1991) proposed a neuropathological staging to differentiate initial, intermediate, and advanced AD based on the spread of NFTs within the MTL memory circuit: Braak stage 0 corresponds to an absence of NFTs, stages I–II displays NFTs within the entorhinal-perirhinal cortex, stages III–IV shows NFTs additionally in hippocampus and, stages V–VI, NFTs are widely distributed in neocortical areas. Although previous studies evaluated the association between the Consortium to Establish a Registry in Alzheimer's Disease (CERAD; Mirra, 1997) and NIA-Reagan AD (The National Institute on Aging) pathologic criteria and clinical findings in older people without cognitive impairment (Bennett et al., 2002; Guillozet et al., 2003; Markesbery, 2010; Morris and Price, 2001; Morris et al., 2001), there is limited information on the relationship between Braak staging and longitudinal neurocognitive measure changes in this type of population (Bennett et al., 2002; Erten-Jones et al., 2009; Guillozet et al., 2003; Markesbery, 2010; Morris et al., 2001; Mufson et al., 1999; Nelson et al., 2009).

Previously, we performed clinical molecular pathobiological investigations regarding the onset of dementia in the elderly using tissue obtained from the Rush Religious Orders Study (RROS), a longitudinal clinic-pathologic investigation of aging and AD (Mufson et al., 1999, 2008, 2012b). In these studies, subjects with a premortem clinical diagnosis of NCI were classified postmortem with a wide range of Braak scores (I–V) (Gilmor et al., 1999; Mufson et al., 1999, 2012b; Perez et al., 2015). Recently, we reported in a cross-section study that elderly RROS participants without dementia and free of other neurological disorders or pathologies who at autopsy were classified as Braak, NFT stages of I–V displayed preserved cognitive function (Mufson et al., 2016). Here, we extend this investigation to a longitudinal examination of changes in

* Corresponding author at: Alzheimer's Disease Research Laboratory, Department of Neurobiology, Barrow Neurological Institute, 350 W. Thomas RD., Phoenix, AZ 85013, USA. Tel.: 602-406-8525; fax: 602-406-8520.
E-mail address: elliott.mufson@dignityhealth.org (E.J. Mufson).

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.03.003

cognitive domains in this cohort of cases grouped by Braak stage. Linear mixed effects models were used to assess differences in the trajectory of change for cognitive composite scores between the Braak stage groups and to determine the association between amyloid load and neuritic and diffuse plaque counts with longitudinal changes in episodic memory and executive function.

2. Methods

Braak staging and cognitive status were examined in 106 older deceased and autopsied persons with no cognitive impairment and no coexisting clinical or neurological condition judged to contribute to cognitive impairment at the last clinical evaluation (Bennett et al., 2005; Mufson et al., 1999). The participants agreed to annual clinical evaluations and signed an informed consent and an Anatomic Gift Act donating their brains at time of death (see Table 1). Data from these subjects have been used in numerous clinical pathologic studies supported by our ongoing NIA program project grant entitled the "Neurobiology of Mild Cognitive Impairment in the Elderly" (PO1AG14449) over the last almost 20 years. Individuals were chosen from all RROS brains that came to autopsy during a rolling admission (Bennett et al., 2006). Neuropathological procedures used to determine these conditions have been reported (Bennett et al., 2004, 2005, 2006). The cases chosen for this study were derived from the RROS cohort based on a strict exclusion criteria. Cases with small or large vascular infarcts, strokes, Parkinson's disease, Lewy body pathology, or hippocampal sclerosis were excluded. In addition, those taking anticholinesterases or medication for depression were also excluded. The average interval from last evaluation to brain autopsy was 0.73 + 0.79 years. The Human Investigation Committee of Rush University Medical Center approved the study.

2.1. Clinical evaluation

Participants underwent a uniform, structured, clinical evaluation, and self-report medical history obtained by a team led by a neurologist, and cognitive function was determined by a trained neuropsychological test technician (Bennett et al., 2005, 2006). Medications used by the subjects within the previous 14 days of the examination were reviewed and classified. After review of all clinical data and examination of the participant, a clinical diagnosis was made by a board-certified neurologist or geriatrician with expertise in the evaluation of elderly persons with dementia. Diagnostic classification of no cognitive impairment was performed as described previously (Bennett et al., 2005, 2006). A neurologist reviewed the medical history, medication use, neurologic examination, results of cognitive performance testing, and the neuropsychologist's opinion of cognitive impairment and dementia. Each participant was evaluated in their home, emphasizing findings deemed clinically relevant.

2.2. Cognitive composite scores

The episodic memory composite (EMC) score was derived from the results of the following tests: WMS-R Logical Memory Story, Immediate and Delayed Recall, CERAD Word List Immediate Recall, CERAD Word List Delayed Recall, CERAD Word List Recognition. The executive function composite (EFC) used the symbol digit modalities test, category fluency test, and Raven's progressive matrices. Composite scores were derived by first converting raw test scores into z-scores using the sample mean and sample standard deviation for each test. The resulting z-scores from each test were then averaged to create the composite score (episodic memory and executive function). The global cognitive score (GCS) was created by taking an average of the episodic and executive composite scores.

2.3. Tissue accruement and neuropathological diagnosis

Brain accruement and processing have been described previously (Mufson et al., 1999). Briefly, 1 hemisphere of the brain was cut into 1 cm thick coronal slabs using a plastic brain slicer and immersion fixed in 4% paraformaldehyde for at least 72 hours. Tissue blocks including the mid-frontal cortex, middle or superior temporal cortex, entorhinal cortex, hippocampus, inferior parietal cortex were paraffin embedded and cut at 6 μm. Examination for cerebral infarctions was conducted on these fixed slabs (Bennett et al., 2006), and the Bielschowsky silver stain was used to visualize neuritic plaques (NPs), diffuse plaques (DPs), and NFTs (Schneider et al., 2009). Paired helical filament tau (AT8; 1:800, Covance) immunohistochemistry (Bennett et al., 2004) was also used to label NFTs and for quantitation (see in the following). Other blocks were used to collect data on amyloid load from the hippocampus and entorhinal cortex. Sections were stained for amyloid load using Aβ antibodies (6 F/3D, 1:50; DAKO, CA, USA and 4G8, 1:9000, Covance, WI, USA) (Bennett et al., 2004). Neuropathological diagnoses were determined according to CERAD (Mirra et al., 1991) and Braak staging (Braak and Braak, 1991; Braak et al., 2006) as recommended by the NIA-Reagan criteria (1997).

2.4. Pathologic quantitation

A board-certified neuropathologist or trained technician blinded to all clinical data counted total number of NPs, DPs, and NFTs in 1 square mm area (100× magnification) per cortical region examined as reported previously (Mufson et al., 1999). Quantitation of amyloid load was performed using a scheme to capture images of Aβ-stained sections employing a custom algorithm as described previously (Mitchell et al., 2000). Briefly, after camera and illumination calibration, 24-bit color images obtained at each sampling site were converted to 8-bit gray scale images. Calculation of percent area occupied by Aβ immunopositive pixels using the public domain Object-Image 1.62p15. This analysis algorithm segmented labeled images and background compartments using 1 of 2 histogram-dependent automatic thresholding methods (iterative self-organizing data analysis) and triangulation. The percent areas for each section were averaged and the number used for analyses. Because the distribution of plaques and NFTs count values did not follow a normal distribution, standardized plaque and tangle count from each area were converted to standard scores by dividing the standard deviation of mean raw counts per marker and region from the entire deceased cohort. Scaled scores for NPs and DPs and NFTs for each region were averaged across the 4 brain regions examined to develop a summary AD pathology score for each subject. Cronbach's coefficient alpha, a measure of internal consistency, was 0.90 for the 12 postmortem indices, supporting the formation of the global measure of AD pathology.

After pathologic evaluation, the cases were divided into 3 groups based on each individual's Braak score (0 to II, III, IV to V). None of the individuals in the sample had a Braak stage of VI.

2.5. Statistical analysis

Chi-square analyses were used to determine significant differences in gender and apolipoprotein E (APOE) ε4 allele status among the different clinical groups. The nonparametric Kruskal–Wallis test was used to examine differences in age at death, education, and postmortem interval between the Braak stage groups.