ELSEVIER

Alzheimer's & Dementia 10 (2014) e1-e8

Alzheimer's & Dementia

Online Exclusives

Fibrillar amyloid correlates of preclinical cognitive decline

Cynthia M. Stonnington[a,*], Kewei Chen[b], Wendy Lee[b], Dona E. C. Locke[a], Amylou C. Dueck[c], Xiaofen Liu[b], Auttawut Roontiva[b], Adam S. Fleisher[b,e], Richard J. Caselli[d], Eric M. Reiman[b]

[a]*Department of Psychiatry & Psychology, Mayo Clinic in Arizona, Scottsdale, AZ, USA*
[b]*Banner Alzheimer's Institute, Phoenix, AZ, USA*
[c]*Department of Biostatistics, Mayo Clinic in Arizona, Scottsdale, AZ, USA*
[d]*Department of Neurology, Mayo Clinic in Arizona, Scottsdale, AZ, USA*
[e]*Department of Neurosciences, University of California–San Diego, San Diego, CA, USA*

Abstract

Background: It is not known whether preclinical cognitive decline is associated with fibrillar β-amyloid (Aβ) deposition irrespective of apolipoprotein E (*APOE*) ε4 status.
Methods: From a prospective observational study of 623 cognitively normal individuals, we identified all subjects who showed preclinical decline of at least 2 standard deviations beyond the decline of the entire group in memory or executive function. Fourteen decliners were matched by *APOE* ε4 gene dose, age, sex, and education with 14 nondecliners. Dynamic Pittsburgh compound B (PiB) positron emission tomography (PET) scans, the Logan method, statistical parametric mapping, and automatically labeled regions of interest were used to characterize and compare cerebral-to-cerebellar PiB distribution volume ratios (DVRs), reflecting fibrillar Aβ burden.
Results: At $P < .005$ (uncorrected), decliners had significantly greater DVRs in comparison to nondecliners.
Conclusions: Asymptomatic longitudinal neuropsychological decline is associated with subsequent increased fibrillar amyloid deposition, even when controlling for *APOE* ε4 genotype.

Keywords: Preclinical; Alzheimer's disease; Amyloid imaging; Cognitive decline; Apolipoprotein E

1. Introduction

There is a growing interest in identifying the earliest preclinical measurements to diagnose Alzheimer's disease (AD) when the disease may not yet be irreversibly established and most amenable to treatment and prevention [1]. We previously demonstrated abnormally declining memory scores on longitudinal neuropsychological tests preceding symptoms of memory loss in a group of healthy volunteers and found that *APOE* ε4 genotype—a known AD susceptibility gene—influenced the age of onset and pattern of this asymptomatic, preclinical decline [2,3]. Furthermore, even when controlling for *APOE* ε4 genotype, individuals with preclinical memory decline showed significantly greater correlations between cerebral hypometabolism in AD-affected brain regions, as measured by a baseline fluorodeoxyglucose (FDG) positron emission tomography (PET), and subsequent verbal memory decline than nondecliners [4].

Fibrillar β-amyloid (Aβ) imaging, most notably with [^{11}C]-benzothiazole radiotracer Pittsburgh compound B (PiB) PET [5] and more recently with the fluorine-18-labeled tracers such as Florbetapir [6], has emerged as a potential biomarker for preclinical AD. Evidence suggests that increases in fibrillar Aβ deposition precede neuronal injury [7,8], and fibrillar amyloid deposition is a potential predictor of later symptomatic cognitive decline [9]. In this study, we were interested in validating the value of asymptomatic longitudinal neuropsychological test score change as a marker for preclinical AD by associating it with PiB retention. We predicted that in cognitively normal middle-aged to elderly persons, despite the relationship between preclinical fibrillar Aβ burden and *APOE* gene dose [10,11], the cohort with greater preclinical cognitive

*Corresponding author. Tel.: 480-301-4853; Fax: 480-301-6258.
E-mail address: stonnington.cynthia@mayo.edu

1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2013.01.009

decline on neuropsychological testing would show increased PiB retention relative to the nondecliners even when matched for *APOE* ε4 genotype, age, sex, and education.

2. Methods

2.1. Study participants

Participants in this study were drawn from the Arizona *APOE* Cohort, a group of healthy individuals who are from Maricopa County (Arizona) selected on the basis of *APOE* genotype and who undergo longitudinal neuropsychological assessment every 2 years [12]. They were mostly 50 to 69 years old at entry and recruited through local newspaper advertisements that requested healthy individuals who had a first-degree relative with AD. Genetic determination of *APOE* allelic status was performed using a polymerase chain reaction-based assay [13]. Screening tests for the longitudinal study included medical history, neurologic examination, Folstein Mini-Mental State Examination (MMSE), Hamilton Depression Rating Scale, and the Structured Psychiatric Interview for *Diagnostic and Statistical Manual of Mental Disorders* (3rd edition, revised). None met criteria for mild cognitive impairment (MCI) [14], AD [15], any other form of dementia, or major depressive disorder [16] at entry. Every 2 years, subjects completed a 4-hour battery of neuropsychological tests, divided into five cognitive domains with four different tests per domain.

Consistent with our previous definition of preclinical decline [2,4], we identified all individuals enrolled in our longitudinal study who had completed at least two consecutive epochs of testing, remained cognitively normal, and fulfilled our defined criteria for amnestic and/or executive preclinical decline. Annualized test-retest change was calculated for each score on each test in the memory and executive functioning domains between epochs. "Decline" was defined a priori as a score declining at least 2 standard deviations (SDs) beyond the decline of the entire group. Table 1 provides detailed information on the decline criteria for each test score. For example, on the Rey Complex Figure Test (CFT) recall, the sample as a whole demonstrated an average improvement in score of 0.27 (SD = 2.69) points per year. Thus, to be labeled as having declined on that particular test score, the subject would have to demonstrate a decline in test score of 5.11 points per year (mean change–2 SD or 0.27–5.38). "Decliners" were individuals who evidenced decline in scores on two different memory tests and/or two different executive function tests. Table 2 shows on which tests and scores each subject declined and what the subject's specific amount of per year decline was on that test score. "Nondecliners" were defined as individuals who did not experience such per-year decline. Memory domain measures included Auditory Verbal Learning Test (short-term memory, long-term memory, or percent recall), Selective Reminding Test free recall, CFT recall, and Visual Retention Test (VRT) total correct.

Table 1
Criteria for decline on each cognitive measure

Test score	Mean change (SD)*	Mean–2.0 SD†
Memory measures		
CFT recall	0.27 (2.69)	−5.11
AVLT STM	−0.001 (1.26)	−2.26
AVLT LTM	−0.0009 (1.27)	−2.54
AVLT % recall	−0.10 (9.77)	−19.64
VRT	0.0006 (0.88)	−1.76
SRT Free	0.63 (4.03)	−7.42
Executive functioning measures		
WAIS FFD	0.14 (4.17)	−8.19
COWA	0.45 (4.12)	−7.79
WCST cat	−0.10 (0.79)	−1.68
WCST err	0.79 (8.30)	17.39‡
WCST per	0.33 (4.58)	9.49‡
PASAT 3	0.47 (4.15)	−7.84
PASAT 2	1.23 (4.38)	−7.54

Abbreviations: CFT recall, Rey Complex Figure Test delayed recall; AVLT STM, Rey Auditory Verbal Learning Test short-term recall; AVLT LTM, AVLT long-term recall; AVLT long-term percent retention; VRT, Benton Visual Retention Test; SRT free, Selective Reminding Test free recall; WAIS FFD, Wechsler Adult Intelligence Scale Freedom From Distractibility; COWA, Controlled Oral Word Association Test; WCST cat, Wisconsin Card Sorting Test categories completed; WCST err, WCST errors; WCST per, perseverative errors; PASAT 3, Paced Auditory Serial Attention Test 3-second trial; PASAT 2, PASAT 2-second trial.

*Mean (SD) amount of per year change in test score for the entire sample.

†Amount of change in test score that is 2.0 SD below the mean and therefore amount of change required to label as decline on that test score.

‡These are positive scores because higher scores indicate more errors and therefore a poorer performance.

Executive domain measures included Wechsler Adult Intelligence Scale-Revised Freedom from distractibility, Controlled Oral Word Association Test, Wisconsin Card Sorting Test (categories completed, total errors, or perseverative errors), and Paced Auditory Serial Attention Task (3- and 2-second administration).

From the group of 623 cognitively normal participants, we identified an initial list of 30 individuals who fit our definition of decline. Of these, 16 refused participation, had medical contraindications to participation, or had since moved away. The remaining 14 individuals had previously consented for the longitudinal study or prospectively agreed for this study to undergo PiB PET scanning, and each of these decliners was then matched by *APOE* genotype, age, sex, and education to an individual in the nondecliner group who also consented to PiB PET scanning (14 with amnestic and/or executive preclinical decline and 14 nondecliners). All 28 individuals (6 ε4 homozygotes, 6 ε4 heterozygotes, and 16 ε4 noncarriers) gave their written informed consent according to the Declaration of Helsinki, and the Mayo Clinic and Banner Health Institutional Review Boards approved the study.

2.2. Fibrillar Aβ PET

Fibrillar Aβ PET was performed at the Banner Alzheimer's Institute/Banner Good Samaritan Regional