Alzheimer's & Dementia 10 (2014) 690-703

Biomarker progressions explain higher variability in stage-specific cognitive decline than baseline values in Alzheimer disease

Hiroko H. Dodge[a,b,c,*], Jian Zhu[d], Danielle Harvey[e], Naomi Saito[e], Lisa C. Silbert[a,f], Jeffrey A. Kaye[a,f], Robert A. Koeppe[g], Roger L. Albin[b,c,h], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Neurology, Layton Aging and Alzheimer's Disease Center, Oregon Health & Science University, Portland, OR*
[b]*Department of Neurology, University of Michigan, Ann Arbor, MI*
[c]*Michigan Alzheimer's Disease Center, University of Michigan, Ann Arbor, MI*
[d]*Department of Biostatistics, University of Michigan, Ann Arbor, MI*
[e]*Department of Public Health Sciences, University of California, Davis, CA*
[f]*Portland Veteran Affairs Medical Center, Portland, OR*
[g]*Department of Radiology, University of Michigan, Ann Arbor, MI*
[h]*Neurology Service and Geriatric Research, Education and Clinical Center, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI*

Abstract

Background: It is unknown which commonly used Alzheimer disease (AD) biomarker values—baseline or progression—best predict longitudinal cognitive decline.

Methods: 526 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI composite memory and executive scores were the primary outcomes. Individual-specific slope of the longitudinal trajectory of each biomarker was first estimated. These estimates and observed baseline biomarker values were used as predictors of cognitive declines. Variability in cognitive declines explained by baseline biomarker values was compared with variability explained by biomarker progression values.

Results: About 40% of variability in memory and executive function declines was explained by ventricular volume progression among mild cognitive impairment patients. A total of 84% of memory and 65% of executive function declines were explained by fluorodeoxyglucose positron emission tomography (FDG-PET) score progression and ventricular volume progression, respectively, among AD patients.

Conclusions: For most biomarkers, biomarker progressions explained higher variability in cognitive decline than biomarker baseline values. This has important implications for clinical trials targeted to modify AD biomarkers.

Keywords: ADNI; Cognitive declines; Biomarker; Biomarker progressions; ADNI-mem; ADNI-exe; MCI; FDG-PET; MRI volume

1. Introduction

The cascade model of Alzheimer's disease (AD) pathologic progression hypothesizes a specific sequence of pathologic events involving the formation of amyloid-based neuritic plaques, now accepted to occur many years before symptomatic onset, followed by tau-based neurofibrillary pathology, changes in brain structure and function, and finally cognitive impairment and functional disability. This model remains hypothetical with the timing

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Corresponding author. Tel.: 503-494-6977; Fax: 503-494-7499.
E-mail address: dodgeh@ohsu.edu

1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2014.04.513

Table 1
Baseline characteristics of samples (from ADNI 1)

	Normal at baseline			MCI at baseline			AD at baseline		
	N*	Number of assessments available, mean (range)	Baseline values, mean (SD)	N*	Number of assessments available, mean (range)	Baseline values, mean (SD)	N*	Number of assessments available, mean (range)	Baseline values, mean (std)
Age	156	N/A	75.0 (4.8)	262	N/A	74.2 (7.4)	108	N/A	74.0 (7.7)
Years of education	156	N/A	16.0 (2.8)	262	N/A	15.6 (3.0)	108	N/A	14.4 (3.1)
Female (%)	156	N/A	51.0	262	N/A	42.1	108	N/A	54.0
Apoe 4 (e4 allele present) (%)	156	N/A	28.2	262	N/A	55.3	108	N/A	67.6
CSF t-tau (pg/mL)	79	1.8 (1–2)	69.4 (30.1)	131	1.7 (1–2)	104.1 (51.9)	61	1.5 (1–2)	120.3 (48)
CSF Aβ42 (pg/mL)	79	1.8 (1–2)	206.4 (50.5)	131	1.7 (1–2)	168 (58.5)	61	1.5 (1–2)	142.4 (38.3)
FDG-PET	71	3.8 (1–5)	1.3 (0.1)	136	4.1 (1–6)	1.2 (0.1)	53	2.8 (1–4)	1.1 (0.1)
Brain volume (cm^3)									
WMH	156	3.4 (1–5)	7.4E−4 (2E−3)	262	3.6 (1–5)	8.5E−4 (3E−3)	107	2.5 (1–3)	1.1E−3 (3E−3)
Hippocampal	156	4.2 (1–5)	3.4 (0.4)	262	4.3 (1–6)	2.9 (0.5)	108	2.9 (1–4)	2.6 (0.5)
Ventricular	155	4.2 (1–5)	16.6 (8.9)	262	4.3 (1–6)	19.3 (9.6)	108	2.9 (1–4)	22.2 (10.7)
Total brain	156	4.2 (1–5)	1058.4 (107.6)	262	4.3 (1–6)	1046.7 (115.2)	108	2.9 (1–4)	1000.6 (116.0)
WMH/ICV	156	3.3 (1–4)	5E−5% (1.6E−4%)	262	3.6 (1–5)	6E−5% (1.8E−4%)	107	2.5 (1–3)	7E−5% (1.6E−4%)
Hippocampal/ICV	156	4.2 (1–5)	0.2% (0.03%)	262	4.3 (1–6)	0.2% (0.03%)	108	2.9 (1–4)	0.2% (0.03%)
Ventricular/ICV	155	4.2 (1–5)	1.1% (0.5%)	262	4.3 (1–6)	1.3% (0.6%)	108	2.9 (1–4)	1.5% (0.7%)
Total brain/ICV	156	4.2 (1–5)	68.8% (4.0%)	262	4.3 (1–6)	66.7% (4.2%)	108	2.9 (1–4)	65.1% (4.2%)
Thickness (mm)									
Precuneus thickness	156	4.2 (1–5)	2.1 (0.2)	262	4.3 (1–6)	2.0 (0.2)	108	2.9 (1–4)	1.95 (0.2)
Medial temporal thickness†	156	4.2 (1–5)	6.0 (0.5)	262	4.3 (1–6)	5.4 (0.8)	108	2.9 (1–4)	4.9 (0.7)

Abbreviations: CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment; WMH, white matter hyperintensity; ICV, intracranial volume.

*N at baseline.

†Summary variable by adding averaged means for left and right entorhinal, perirhinal, and posterior parahipplocampal cortical region thickness.

of each stage in relation to disease progression yet to be confirmed. Accumulated data, however, support this model and it provides a useful framework for investigating the properties of different biomarkers [1,2]. Clinical trials would be improved by identifying the biomarkers most strongly associated with cognitive and functional declines at each stage of AD. Identifying biomarkers associated with subtle declines in cognitive functions among cognitively normal and mildly affected subjects is especially critical as research efforts move toward early identification of high risk subjects and prevention of progression.

One issue not examined systematically across various biomarkers is which component of commonly used AD biomarkers—baseline value or progression of biomarker values (biomarker progressions)—is more strongly associated with cognitive declines. In the cascade model [1,2], the capacity of each biomarker to predict cognitive decline depends on the stage of AD disease process (e.g., normal, early mild cognitive impairment [MCI], late MCI, or AD), and whether biomarker baseline values or biomarker progressions are used. It is likely, for example, that brain beta amyloid burden is already high and probably plateaus by the time of AD diagnosis [3,4], and although brain amyloid burden may distinguish among subjects with AD, MCI, and normal subjects cross-sectionally, continuing declines in cognitive functions at late MCI or AD stages will not be related to brain amyloid burden. Although baseline biomarker values are examined often in relation with subsequent longitudinal cognitive or functional trajectories, there is a paucity of data regarding biomarker progressions and their associations with cognitive or functional trajectories. Examining the relative ability of baseline values versus biomarker progressions at each stage of AD in explaining cognitive trajectories could improve clinical trial designs by allowing the recruitment of high risk populations with higher accuracy. We used data from the Alzheimer's Disease Neuroimaging Initiative study (ADNI-1) to examine which components (baseline values or biomarker progressions) are associated with declines in memory and executive cognitive functions. To conduct a fair comparison across different biomarkers and to increase clinical applicability of our results, we standardized all biomarkers and provided the clinical values corresponding to each standard deviation.

2. Methods

2.1. Data source

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public–private partnership. The primary goal of