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Subtypes based on cerebrospinal fluid and magnetic resonance imaging markers in normal elderly predict cognitive decline

J. Nettiksimmons[a], D. Harvey[a], J. Brewer[b], O. Carmichael[c], C. DeCarli[c], C.R. Jack Jr[d], R. Petersen[d], L.M. Shaw[e], J.Q. Trojanowski[e], M.W. Weiner[e], L. Beckett[a,*], The Alzheimer's Disease Neuroimaging Initiative[†]

[a] *Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Davis, CA 95616, USA*
[b] *Departments of Radiology and Neurosciences, University of California, San Diego, La Jolla, CA 92093-0949, USA*
[c] *Department of Neurology, University of California, Davis, Davis, CA 95616, USA*
[d] *Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN, USA*
[e] *Institute on Aging, Alzheimer's Disease Core Center, Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[e] *Center for Imaging of Neurodegenerative Diseases, University of California, San Francisco, San Francisco, CA, USA*

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Abstract

Cerebrospinal fluid (CSF) and structural magnetic resonance imaging (MRI) show patterns of change in Alzheimer's disease (AD) that precede dementia. The Alzheimer's Disease Neuroimaging Initiative (ADNI) studied normal controls (NC), subjects with mild cognitive impairment (MCI), and subjects with AD to identify patterns of biomarkers to aid in early diagnosis and effective treatment of AD. Two hundred twenty-two NC underwent baseline MRI and clinical examination at baseline and at least one follow-up. One hundred twelve also provided CSF at baseline. Unsupervised clustering based on initial CSF and MRI measures was used to identify clusters of participants with similar profiles. Repeated measures regression modeling assessed the relationship of individual measures, and of cluster membership, to cognitive change over 3 years. Most individuals showed little cognitive change. Individual biomarkers had limited predictive value for cognitive decline, but membership in the cluster with the most extreme profile was associated with more rapid decline in ADAS-cog. Subtypes among NC based on multiple biomarkers may represent the earliest stages of subclinical cognitive decline and AD.

Keywords: Alzheimer's disease; Dementia; Early diagnosis; Cerebrospinal fluid; Tau protein; Amyloid beta-protein; Structural magnetic resonance imaging; Hippocampal volume; Cognition; Clustering; Normal controls

Alzheimer's disease (AD) is a neurocognitive disorder currently estimated to affect some five million people in the USA and more than 25 million worldwide (Brookmeyer et al., 2007; Evans et al., 1990; Harvey et al., 2003; Hebert et al., 2003). Mild cognitive impairment (MCI) has gained recognition as an intermediate clinical category between normal cognitive function and AD, with a greatly increased risk of onset of AD (Bennett et al., 2002; Petersen et al., 2009). AD is characterized not only by cognitive decline, but also by underlying neurobiological changes that likely precede the diagnosis of AD by a considerable period, during MCI and possibly even earlier, before measurable clinical impairment. The process is hypothesized to begin with amyloid deposition, followed by cortical atrophy and decreased metabolism, with effects only gradually becom-

* Corresponding author at. Tel.: (530) 754-7161; fax: (530) 752-3239.
E-mail address: labeckett@ucdavis.edu (L. Beckett).

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ing apparent in decreased cognitive performance and function (Jack et al., 2010). Identification of early markers of disease would be of great interest to facilitate early diagnosis, improved clinical trials for prevention by targeting individuals at greatest risk, and, ultimately, effective treatment before widespread irreversible neurodegeneration (Clark et al., 2008).

A large number of potential markers have been proposed, including volumetric measures based on magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) biomarkers, FDG PET and others (Hampel et al., 2007; Shaw et al., 2007). Cortical atrophy, for example, is evident on structural MRI not only in AD but also to some extent in people with MCI (Morra et al., 2009; Nestor et al., 2008) and in normal elderly before the onset of MCI (Carlson et al., 2008). Between-person differences in CSF protein levels have also been reported to be associated with AD and MCI (Clark et al., 2008; Maddalena et al., 2003; Shaw et al., 2009). White matter hyperintensity (WMH) has been reported to be increased in patients with AD, suggesting that vascular lesions may also play a role in the neurodegenerative process (Barber et al., 1999). Alternatively, WMH may be a vascular pathology contributing to cognitive impairment in an additive or even multiplicative manner. Homocysteine, a risk factor for vascular damage, has also been hypothesized as a possible risk factor for dementia (Smith, 2008). Most studies of markers have focused on AD and MCI, as the clinical decline is most evident in these groups and association of candidate markers with clinical benchmarks is more readily established. An earlier biomarker horizon, however, would be of great scientific interest and have substantial clinical relevance.

The Alzheimer's Disease Neuroimaging Initiative (ADNI), jointly funded by NIH, pharmaceutical partners, and the Alzheimer's Association, is a multisite research initiative whose aim is to identify biomarkers that would allow the pathological changes of AD to be diagnosed earlier, well before the clinical criteria for dementia are met, and to be tracked more precisely. The goal is to provide earlier diagnosis and better assessment of disease progression and response to therapy. The ADNI participants included normal controls (NC) with detailed standardized assessment of many potential candidate biomarkers and longitudinal follow-up of cognitive outcomes for up to 3 years. We examined a set of imaging and cerebrospinal fluid measures previously proposed in the literature as candidate markers for early diagnosis, and assessed their distribution in normal controls and their relationship to cognitive outcomes over the follow-up period. Our hypothesis was that despite cognitive homogeneity at baseline in the NC subjects, there would be underlying biological heterogeneity in candidate markers, reflecting the earliest detectable changes in the brain. These biological differences would be correlated with each other in a structured way, leading to the ability to construct subgroups based on markers alone, and such subgroups would subsequently have different cognitive trajectories.

1. Methods

1.1. The Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit organizations, as a US$60 million, 5-year public-private partnership. The research plan called for recruiting 800 adults, ages 55 to 90: approximately 200 healthy elderly controls, 400 subjects with MCI, and 200 subjects with mild but probable AD. Subjects are followed longitudinally for up to 3 years, with MRI scans, complete cognitive testing, and blood/urine samples collected at 6-month intervals, depending on baseline diagnosis. In addition, subsets of the subjects undergo FDG-PET scans and CSF collection and testing (Mueller, 2005a; Mueller, 2005b).

1.2. Subjects

The individuals studied were recruited between 17 August 2005 and 4 September 2007 as ADNI participants and were identified at baseline clinical evaluation as cognitively normal. NC, MCI and AD participants were frequency-matched by age-group to a common target age profile. NC participants underwent cognitive testing and clinical examination by a physician at baseline and every 6 months for the first year and then annually for the next 2 years. MRI scans (1.5 Tesla) were performed in each subject (www.loni.ucla.edu/ADNI/Research/Cores/index.shtml) at baseline, repeated at 6, 12, 24, and 36 months. Approximately half the participants also provided CSF at the baseline and m12 visits. Additional details are given in Petersen et al. (Petersen et al., 2010). This study was approved by the Institutional Review Boards of all the participating institutions. Informed written consent was obtained from all participants at each site. A detailed description of the study design and inclusion criteria is available at clinicaltrials.gov/show/NCT00106899. Data used in this analysis were downloaded from the ADNI database (www.loni.ucla.edu/ADNI) on 27 September 2009. Analysis focused on NC but the MCI and AD group were described at baseline for comparison purposes.

1.3. Measures

Biomarker summary measures for cluster analysis were selected using a list initially specified by researchers from the ADNI Imaging and Biomarker Cores at the time of grant submission, for core hypothesis tests. MRI summary measures were calculated by the Anders Dale Laboratory at UC San Diego and normalized by their measure of intracranial