

Toward a multifactorial model of Alzheimer disease

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Abstract

Relations among antecedent biomarkers of Alzheimer disease (AD) were evaluated using causal modeling; although correlation cannot be equated to causation, causation does require correlation. Individuals aged 43 to 89 years ($N = 220$) enrolled as cognitively normal controls in longitudinal studies had clinical and psychometric assessment, structural magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) biomarkers, and brain amyloid imaging via positron emission tomography with Pittsburgh Compound B (PIB) obtained within 1 year. CSF levels of $A\beta_{42}$ and tau were minimally correlated, indicating they represent independent processes. $A\beta_{42}$, tau, and their interaction explained 60% of the variance in PIB. Effects of *APOE* genotype and age on PIB were indirect, operating through CSF markers. Only spurious relations via their common relation with age were found between the biomarkers and regional brain volumes or cognition. Hence, at least 2 independent hypothesized processes, one reflected by CSF $A\beta_{42}$ and one by CSF tau, contribute to the development of fibrillar amyloid plaques preclinically. The lack of correlation between these 2 processes and brain volume in the regions most often affected in AD suggests the operation of a third process related to brain atrophy.

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1. Introduction

It is increasingly accepted that the pathologic changes that lead to the eventual diagnosis of symptomatic Alzheimer disease (AD) begin long before there is sufficient cognitive impairment to warrant a clinical diagnosis of the disease (Jack et al., 2009; Price et al., 2009). Recent advances (Klunk et al., 2004) make it possible to image fibrillar amyloid plaques, a pathologic hallmark of AD, providing one avenue to detection of pathology prior to clinical diagnosis.

There is a strong inverse relation between fibrillar amyloid plaque burden as assessed by positron emission tomography (PET) imaging using the amyloid tracer, Pittsburgh Compound-B (PIB), with levels of cerebrospinal fluid

(CSF) $A\beta_{42}$ in cognitively healthy individuals (Fagan et al., 2006, 2009; Tolbloom, 2009). This has been interpreted as suggesting that an early step in the process leading to AD is sequestering of $A\beta_{42}$ in plaques (Hong et al., 2011), thereby reducing the level in the CSF. The amount of plaque burden also is associated with increased levels of CSF total tau and phospho-tau₁₈₁ (ptau; Fagan et al., 2009b). This relation has often been interpreted in terms of the amyloid cascade hypothesis (Selkoe, 1991). In its simplest form the hypothesis states that $A\beta_{42}$ peptides aggregate to form amyloid plaques which, in turn, lead to synaptic loss and cell death, reflected in elevated CSF tau, thereby causing dementia. Recent reviews, however, suggest that the process may not be that simple (Holtzman et al., 2011; Hyman, 2011; Pimpalikar, 2009; Small and Duff, 2008).

Other variables associated with one or more of the CSF biomarkers and PIB include age and apolipoprotein (*APOE*)

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genotype, the major genetic susceptibility factor associated with late-onset AD (Morris et al., 2010; Rowe et al., 2010; Sunderland et al., 2004; Vemuri et al., 2010). Mixed results have been reported for forebrain structure (Apostolova et al., 2010; Becker et al., 2011; Chetelat et al., 2010; Fagan et al., 2009a; Mormino et al., 2009; Oh et al., 2011; Tosun et al., 2010). Concurrent measures of cognition, however, are uncorrelated with the CSF measures (Fagan et al., 2009) or PIB (Mormino et al., 2009; Oh et al., 2011; Storandt et al., 2009) in cognitively normal individuals.

We examined all of these variables in cognitively normal individuals using causal modeling in an effort to explore theoretical models of their interrelations. To the best of our knowledge there has been no prior attempt to do so. Causal modeling is a statistical procedure using regression analysis that is designed to determine if empirical data are consistent with a theoretical model. It requires that 3 conditions exist if X is a potential cause of Y (Cohen et al., 2003). One, there must be a correlation between X and Y; that is, although correlation cannot be equated to causation, causation does require correlation. Two, X must precede Y in time. Three, the relation between X and Y must not be spurious; a spurious relation is one in which X and Y are related because both are influenced by a third variable, Z. For example, wrinkled skin and slowed reaction times are correlated because both are associated with age, not because either causes the other. Of course, although correlation cannot be equated to causation, causation does require correlation.

Longitudinal study ultimately is required to verify causality, but those results for preclinical AD may not be available for many years. Similarly, longitudinal study is necessary to determine the temporal order of appearance of the various processes, even if they are independent. In the meantime, models built on cross-sectional data can provide useful suggestions about avenues of investigation of various underlying pathophysiological processes.

2. Methods

2.1. Participants

The sample included 220 participants (64% women) aged 45 to 89 years ($M = 65.8$, $SD = 9.7$) enrolled in longitudinal studies at the Knight Alzheimer's Disease Research Center, Washington University in St Louis. Their mean years of education was 15.7 years ($SD = 2.6$). Only participants with PIB imaging and lumbar puncture (LP) to obtain CSF within 1 year of each other ($M = 1.7$ months, $SD = 4.4$) between December 2003 and April 2010 were included. Participants were cognitively normal (Clinical Dementia Rating [CDR] = 0; Morris, 1993) at the time of assessment; 14 subsequently progressed to a CDR > 0 indicating cognitive impairment. A subset ($n = 164$) comparable to the total sample in terms of age, gender, education, and *APOE* allele distribution had structural brain as-

essment with magnetic resonance imaging (MRI) within 1 year of LP ($M = 1.2$ months, $SD = 3.6$) and PIB imaging ($M = 0.7$ months, $SD = 2.9$). All procedures were approved by the university's Human Research Protection Office; written informed consent was obtained from participants and their collateral sources. Data from many of these participants have appeared in previous reports from the center.

2.2. Clinical evaluation

Experienced clinicians determined if the person was demented (CDR > 0) or not (CDR = 0) based solely on semistructured interviews with participants and their knowledgeable collateral sources (usually spouse or adult child) followed by a neurological examination of the participant. Clinicians determined if any cognitive problems represented decline from former level of function for that individual and interfered to some degree with the person's ability to carry out accustomed activities. Assessment included a health history, medication inventory, and assessment of depression and aphasia. Clinicians were unaware of the results of previous clinical evaluations and of previous and current psychometric test results. The CDR staging and diagnostic protocol is sensitive to clinical progression and highly predictive (93%) of autopsy-confirmed AD (Berg et al., 1998).

2.3. CSF collection, processing, and biomarker measurement

CSF (20–30 ml) free from blood contamination was collected by LP in polypropylene tubes at 8:00 AM after overnight fasting as described previously (Fagan et al., 2006). Samples were gently inverted to avoid gradient effects, briefly centrifuged at low speed to pellet any cellular elements, and aliquoted (500 μ l) into polypropylene tubes before freezing at -84 °C. Analyses for $A\beta_{42}$, total tau, and ptau were performed using commercial enzyme-linked immunosorbent assay (INNOTEST; Innogenetics, Ghent, Belgium). Samples were continuously kept on ice with only a single thaw after initial freezing before assays.

2.4. PET PIB imaging

In vivo fibrillar amyloid imaging via PET with PIB ([*N*-methyl- 11 C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole) was performed as described previously (Mintun et al., 2006). Approximately 12 mCi of [11 C]PIB was administered intravenously simultaneous with initiation of a 60-minute dynamic PET scan in three-dimensional mode. Measured attenuation factors and a ramp filter were used to reconstruct dynamic PET images. Three-dimensional regions of interest (ROIs) were created for each participant based on their individual MRI scans (T1-weighted $1 \times 1 \times 1.25$ mm MPRAGE). A binding potential for each ROI was calculated (Logan et al., 1996) to express regional binding values in a manner proportional to number of binding sites. Values from prefrontal cortex, gyrus rectus, lateral temporal, and precuneus ROIs were averaged to calculate a mean cortical binding potential value

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