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Effects of cerebrospinal fluid proteins on brain atrophy rates in cognitively healthy older adults

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ABSTRACT

Biomarkers associated with Alzheimer's disease (AD)–like brain atrophy in healthy individuals may identify mechanisms involved in early stage AD. Aside from cerebrospinal fluid (CSF) β-amyloid42 (Aβ42) and tau, no studies have tested associations between CSF proteins and AD-like brain atrophy. We studied 90 healthy elders, who underwent lumbar puncture at baseline, and serial magnetic resonance imaging scans for up to 4 years. We tested statistical effects of baseline CSF proteins (N = 70 proteins related to Aβ42-metabolism, microglial activity, and synaptic/neuronal function) on atrophy rates in 7 AD-related regions. Besides the effects of Aβ42 and phosphorylated tau (P-tau) that were seen in several regions, novel CSF proteins were found to have effects in inferior and middle temporal cortex (including apolipoprotein CIII, apolipoprotein D, and apolipoprotein H). Several proteins (including S100β and matrix metalloproteinase–3) had effects that depended on the presence of brain Aβ pathology, as measured by CSF Aβ42. Other proteins (including P-tau and apolipoprotein D) had effects even after adjusting for CSF Aβ42. The statistical effects in this exploratory study were mild and not significant after correction for multiple comparisons, but some of the identified proteins may be associated with brain atrophy in healthy persons. Proteins interacting with CSF Aβ42 may be related to Aβ brain pathology, whereas proteins associated with atrophy even after adjusting for CSF Aβ42 may be related to Aβ-independent mechanisms.

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1. Introduction

Alzheimer's disease (AD) leads to severe atrophy of cortical brain tissue and ultimately results in dementia. The disease is believed to have a long pre-symptomatic phase, with brain pathology accumulating before cognitive symptoms. The major disease hallmarks are plaques composed of β-amyloid (Aβ) peptides and neurofibrillary tangles composed of phosphorylated tau proteins (Braak and Braak, 1991). The view that AD starts before any symptoms implies that its earliest changes can be studied only in persons who are cognitively normal. However, longitudinal studies on development of cognitive impairment in healthy persons are limited by the long follow-up time and large study populations needed to detect significant cognitive changes. An alternative is to study longitudinal atrophy of AD-related brain regions, which are predictive of future cognitive decline (Rusinek et al., 2003). Biomarkers predicting such atrophy in cognitively healthy persons may be useful to identify those at risk for AD, and could inform on biological mechanisms during early disease stages.

Biomarker measurements of Aβ pathology, using positron emission tomography (PET) or cerebrospinal fluid (CSF), likely

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.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.

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become abnormal early in AD, even before cognitive symptoms (Bateman et al., 2012; Jack et al., 2010). A few studies have tested whether Aβ pathology predicts longitudinal brain atrophy in cognitively healthy people (Chételat et al., 2012; Fjell et al., 2010; Henneman et al., 2009; Schott et al., 2010; Sluimer et al., 2010; Tosun et al., 2011). Some (Chételat et al., 2012; Fjell et al., 2010; Schott et al., 2010), but not all (Henneman et al., 2009; Sluimer et al., 2010; Tosun et al., 2011), of these studies found that an AD-like CSF or PET Aβ biomarker pattern predicted longitudinal atrophy. Studies showing that Aβ pathology predicts longitudinal AD-like atrophy in cognitively healthy persons are consistent with the "dynamic biomarker model" presented by Jack et al. (Jack et al., 2010), but it should be noted that some studies found Aβ-related atrophy also in areas not typically associated with early AD changes (Fjell et al., 2010).

Early pathological events leading to atrophy in AD may be reflected by other CSF changes besides altered concentrations of the established biomarkers Aβ42 and tau; however, to our knowledge, no previous study has examined whether other CSF proteins are associated with longitudinal AD-like atrophy. Here we used CSF proteomics data from a multiplex panel, together with longitudinal structural magnetic resonance imaging (MRI) data, to identify novel biochemical predictors of AD-related brain atrophy in cognitively healthy elderly participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI). We studied brain regions typically shown to be vulnerable in AD (although it should be noted that widespread atrophy may also be seen in cognitively well-screened and longitudinally stable adults with no signs of Aβ pathology) (Oh et al., 2013). The tested proteins were selected for biological functions possibly altered in early-stage AD (Aβ metabolism, microglial activity, and synaptic/neuronal function). Our primary hypothesis was that baseline protein levels were associated with atrophy rates. Although the dominant view in AD research is that Aβ pathology is the initiator in the neuropathological cascade, Aβ-independent processes have also been proposed (Chételat, 2013; Pimplikar et al., 2010). Based on this, we investigated whether Aβ would influence the relationship between proteins and atrophy rates. We tested the specific hypotheses that some proteins interact with Aβ pathology to affect atrophy rates (suggesting atrophy mechanism linked to Aβ pathology), and that some proteins affect atrophy rates even when adjusting for the presence of Aβ pathology (suggesting atrophy mechanisms that do not depend on Aβ pathology).

2. Methods

2.1. Study design

We examined changes in gray matter volume in a priori–specified regions of interest in cognitively normal individuals. Structural magnetic resonance imaging brain scans at multiple time points (up to 6 time points: ADNI screening, and at 6, 12, 24, 36 ,and 48 months, median 5 scans per participant, range 2–6 scans) were acquired at multiple sites using 1.5 Tesla MRI scanners. With the use of FreeSurfer longitudinal processing framework, regional gray matter volumes were measured at each time point. Linear mixed effects models were performed to test whether baseline CSF protein concentrations (N = 70 different proteins tested separately) were associated with rates of brain atrophy (i.e., the rate of change in volume).

2.2. Participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). 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 not-for-profit organizations, as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and to monitor their effectiveness, as well as to lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 participants, but ADNI has been followed by ADNI-GO and ADNI-2. To date, these 3 protocols have recruited more than 1500 adults 55 to 90 years of age, to participate in the research, consisting of cognitively normal older individuals, persons with early or late MCI, and persons with early AD (for up-to-date information, see www.adni-info.org). The population in this study included ADNI-1 participants with valid results for a CSF multiplex protein panel (described below) and successful longitudinal FreeSurfer processing of MR images from at least 2 time points.

2.3. Structural MRI acquisition

The participants underwent a standardized 1.5 Tesla MRI protocol, which included T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence, as previously described (Jack et al., 2008).

2.4. FreeSurfer longitudinal MR image processing

Automated cortical volume measures and hippocampal segmentation were performed with FreeSurfer software package, version 4.4 (http://surfer.nmr.mgh.harvard.edu/fswiki), as previously described (Fischl et al., 2002, 2004). To reduce the confounding effect of intra-participant morphological variability, each participant's longitudinal data series was processed by FreeSurfer longitudinal workflow (http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing). A previous test–retest study validated that the longitudinal processing provides consistent region of interest segmentation (Reuter et al., 2012). All images underwent standardized quality control procedures (http://www.loni.ucla.edu/twiki/pub/ADNI/ADNIPostProc/UCS-FFreeSurferMethodsSummary.pdf). Participants with complete segmentation failure or gross errors throughout all brain regions were rated as complete failure. Participants with gross errors in 1 or more specific brain regions (i.e., temporal lobe regions, superior regions, occipital regions, and insula) were given partial pass rating. Participants with partial pass rating were included in analyses of appropriate brain regions only. For this study, we used volumetric measurements of entorhinal cortex, hippocampus, inferior parietal cortex, inferior temporal cortex, middle temporal cortex, posterior cingulate cortex, and precuneus (combining left and right hemisphere data).

2.5. CSF biomarker concentrations

A CSF sample was collected at study baseline by lumbar puncture, and shipped to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center for long-term storage at −80 °C. The

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