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Featured Article

Longitudinal brain structural changes in preclinical Alzheimer disease

Jordi Pegueroles[a,b,1], Eduard Vilaplana[a,b,1], Victor Montal[a,b], Frederic Sampedro[a,b,c], Daniel Alcolea[a,b], Maria Carmona-Iragui[a,b], Jordi Clarimon[a,b], Rafael Blesa[a,b], Alberto Lleó[a,b], Juan Fortea[a,b,*], and for the Alzheimer's Disease Neuroimaging Initiative

[a]*Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau- Biomedical Research Institute Sant Pau-Universitat Autònoma de Barcelona, Barcelona, Spain*

[b]*Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, CIBERNED, Spain*

[c]*Nuclear Medicine Department, Hospital de la Santa Creu i Sant Pau—Biomedical Research Institute Sant Pau—Universitat Autònoma de Barcelona, Barcelona, Spain*

Abstract

Background: Brain structural changes in preclinical Alzheimer's disease (AD) are poorly understood.

Methods: We compared the changes in cortical thickness in the ADNI cohort during a 2-year follow-up between the NIA-AA preclinical AD stages defined by cerebrospinal fluid (CSF) biomarker levels. We also analyzed the correlation between baseline CSF biomarkers and cortical atrophy rates.

Results: At follow-up, stage 1 subjects showed reduced atrophy rates in medial frontal areas compared to stage 0 subjects, whereas stage 2/3 subjects presented accelerated atrophy in medial temporal structures. Low CSF $A\beta_{1-42}$ levels were associated with reduced atrophy rates in subjects with normal tau levels and high CSF tau levels with accelerated atrophy only in subjects with low $A\beta_{1-42}$ levels.

Discussion: Our longitudinal data confirm a biphasic trajectory of changes in brain structure in preclinical AD. These have implications in AD trials, both in patient selection and the use of MRI as a surrogate marker of efficacy.

Keywords: Alzheimer's disease; CSF; Biomarkers; Longitudinal; MRI; Amyloid; Tau

1. Background

The asymptomatic phase of Alzheimer's disease (AD) begins decades before the appearance of the first clinical symptoms. The NIA-AA research criteria divided this preclinical phase into three stages [1]: subjects with no evidence of AD biomarker alteration or cognitive decline (stage 0), asymptomatic amyloidosis (stage 1), amyloidosis with evidence of neurodegeneration (stage 2), and amyloidosis, neurodegeneration, and subtle cognitive decline (stage 3).

The data regarding structural brain changes in preclinical AD remain unclear. Several cross-sectional studies have reported cortical thinning [2–7] or hippocampal atrophy [8] in relation to brain amyloidosis, whereas others have found no relationship [9] or even increased cortical thickness [10–12]. Several factors might account for these discrepancies. First, there are important methodological differences across studies such as the age range sampled, preclinical AD definition (i.e., the use of imaging versus biochemical biomarkers) or technical differences in the analysis of the structural changes (i.e., volume vs. surface-based methods).

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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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[1]These authors contributed equally to the manuscript.

*Corresponding author. Tel.: (34)-935565986; Fax: (34)-935565602.

E-mail address: jfortea@santpau.cat

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Second, the relationship between cerebrospinal fluid (CSF) biomarkers and brain structure in preclinical AD might not be linear, possibly reflecting interactions between different processes on brain structure. In this respect, two recent studies reported that brain volume loss in preclinical AD only occurred in subjects with both amyloid and tau biomarker alterations [13,14]. Based on cross-sectional data, we recently proposed that interactions between CSF biomarkers in preclinical AD would follow a 2-phase phenomenon [11]. The first phase would consist of pathologic cortical thickening in relation to decreasing CSF ß-amyloid 1–42 ($Aß_{1–42}$) levels, followed by a second phase of cortical thinning once tau biomarkers in CSF become abnormal.

Longitudinal approaches are needed to further validate this model. However, the number of such studies is limited, and the conclusions are unclear. Likewise to the cross-sectional studies, some groups reported no relationship between CSF $Aß_{1–42}$ and brain structural longitudinal changes [13,15], whereas others showed progressive atrophy in relation with decreased CSF $Aß_{1–42}$ levels [2,16–19]. These discrepancies underline the importance of taking into account the interaction between tau and amyloid pathologies when interrogating the longitudinal brain changes in preclinical AD [13,16]. Furthermore, the study of the cortical dynamics in preclinical AD must also take into account that not all brain changes in aging reflect incipient AD [20]. Brain structure is highly dynamic and evolves with age [21], and it may be difficult to dissect the age-related effects from the disease-specific effects on brain structure [6,20,22–24]. Aging and AD might have overlapping effects on specific regions of the cerebral cortex [20,22]. Therefore, the AD-specific changes should be considered superimposed to the age-related progressive brain atrophy.

In this work, we aimed to confirm the aforementioned two-phase phenomenon in preclinical AD, comparing longitudinal brain structural changes at a 2-year follow-up based on the following hypotheses: stage 1 subjects would show less cortical thinning than stage 0 subjects, whereas stage 2/3 subjects would show accelerated cortical thinning compared to stage 0 subjects.

2. Methods

2.1. Study participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. 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 subjects have been recruited from over 50 sites across the United States and Canada. More information can be found in the Acknowledgments section (see also http://adni-info.org/).

We selected all healthy controls with available CSF results and a 3T MRI study both at baseline and at 2-year follow-up. We also included the 1-year follow-up MRI in the processing stream, when available. We also searched the available CSF data at the 2-year follow-up.

2.2. CSF analysis

CSF acquisition and biomarker concentration measurements using ADNI data have been previously described [25]. $Aß_{1–42}$ and total tau (t-tau) levels were measured using the multiplex xMAP Luminex platform (Luminex) with Innogenetics (INNO-BIA AlzBio3) immunoassay kit–based reagents. Using published cutoffs (192 pg/mL for $Aß_{1–42}$ and 93 pg/mL for tau) [25], we classified all subjects into stage 0 (Aß−/tau−), stage 1 (Aß+/tau−) and stage 2/3 (Aß+/tau+). T-tau was used instead of p-tau because in ADNI, t-tau has a higher specificity than p-tau (92.3% vs. 73.1%) [25]. Only eight subjects did not meet the NIA-AA preclinical staging criteria (Aß−/tau+) and were excluded from further analyses.

The duration of the AD preclinical stages has not been established and might be significant for the aforementioned analyses, especially if it is a period close to or shorter than 2 years. Therefore, for the group comparisons, we conducted two complementary set of analyses. We first performed group analyses in those subjects that at the 2-year follow-up remained in the same CSF category (Aß and t-tau status); termed stage 0 plus, stage 1 plus, or stage 2/3 plus, respectively. We then repeated these analyses using the whole sample of HC with subjects classified into the different preclinical stages based on baseline CSF levels.

2.3. MRI analysis

The details of MRI acquisition and preprocessing are available elsewhere (http://adni-info.org/). All structural MRIs (baseline, 1-year follow-up and 2-year follow-up) were first processed using the cross-sectional cortical reconstruction stream in Freesurfer (v5.1; http://surfer.nmr.mgh.harvard.edu). The procedures have been described previously [26]. All estimated surfaces were visually inspected to detect segmentation errors. Each MRI time-point was then processed with the Freesurfer longitudinal stream [27]. Specifically, an unbiased within-subject template space