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Featured Article

The transitional association between β-amyloid pathology and regional brain atrophy

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Abstract

Introduction: Alzheimer's disease (AD) is characterized by the accumulation of β-amyloid (Aβ) associated with brain atrophy and cognitive decline. The functional form to model the association between Aβ and regional brain atrophy has not been well defined. To determine the relationship between Aβ and atrophy, we compared the performance of the usual dichotomization of cerebrospinal fluid (CSF) Aβ to identify subjects as Aβ+ and Aβ− with a trilinear spline model of CSF Aβ.

Methods: One hundred and eighty-three subjects with mild cognitive impairment and 108 cognitively normal controls with baseline CSF Aβ and up to 4 years of longitudinal magnetic resonance imaging data from the Alzheimer's Disease Neuroimaging Initiative were analyzed using mixed-effects regression. Piecewise-linear splines were used to evaluate the nonlinear nature of the association between CSF Aβ and regional atrophy and to identify points of acceleration of atrophy with respect to Aβ. Several parameterizations of CSF Aβ were compared using likelihood ratio tests and the Akaike information criterion. Periods of acceleration of atrophy in which subjects transition from CSF Aβ negativity to CSF Aβ positivity were estimated from the spline models and tested for significance.

Results: Spline models resulted in better fits for many temporal and parietal regions compared with the dichotomous models. The trilinear model showed that periods of acceleration of atrophy varied greatly by region with early changes seen in the insula, amygdala, precuneus, hippocampus, and other temporal regions, occurring before the clinical threshold for CSF Aβ positivity.

Discussion: The use of piecewise-linear splines provides an improved model of the nonlinear association between CSF Aβ and regional atrophy in regions implicated in the progression of AD. The important biological finding of this work is that some brain regions show periods of accelerated volume loss well before the CSF $A\beta_{42}$ threshold. This implies that signs of brain atrophy develop before the current conventional definition of "preclinical AD".

Keywords: Alzheimer's disease; ADNI; Trilinear; Beta amyloid; Atrophy

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

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1. Introduction

The deposition of fibrillar β-amyloid (Aβ) and accelerated brain atrophy are central features of the development of Alzheimer's disease (AD) [1,2]. Some hypothesize that pathological Aβ metabolism is an initiating event in AD [3]. This is supported by biomarker data, especially in familial forms of AD, where Aβ accumulation occurs many years before brain atrophy and the onset of cognitive impairment [4–7]. Recent studies of controls and subjects with mild cognitive impairment (MCI) have shown early Aβ-related changes in brain structure to occur in both temporoparietal regions and frontal gyri [8–11] and also the thalamus and putamen in subjects with familial AD [12]. However, although Aβ deposition has been shown to be associated with gray matter atrophy, neither the nature of the association nor the functional form, i.e. the statistical parameterization, to model their relationship has been well characterized. Additionally, rates of change of Aβ biomarkers have been shown to increase as subjects approach the clinical threshold that best distinguishes AD patients from controls and subsequently plateau [13–15]. These higher rates of change near the threshold may contribute to the apparent bimodal distribution of Aβ levels in cross-sectional analyses [8,16,17], which has led to the common categorization of subjects into amyloid positive (Aβ+) and amyloid negative (Aβ−) groups. However, little is known about how the transition from Aβ− to Aβ+ relates to brain atrophy or how to model their association. The primary purpose of this study is to compare several parameterizations of CSF Aβ in an attempt to better understand the progression of atrophy.

Several approaches have been used to study the association of Aβ with brain atrophy. One approach is to assume a linear effect of Aβ on atrophy. This model assumes that changes in the level of Aβ are associated with atrophy in the same way regardless of whether subjects have pathological levels of Aβ or not. Another approach and the most common parameterization of Aβ is to dichotomize the continuous form at a threshold that best differentiates subjects with a diagnosis of probable AD from subjects without cognitive impairment. A common threshold used for CSF Aβ measurements in the Alzheimer's Disease Neuroimaging Initiative (ADNI) is 192 ng/L, derived by comparing autopsy-confirmed AD patients with controls [17]. This parameterization assumes a constant atrophy rate in each group with no transition period between them. While these models' simplicity allow for easy interpretation, they are unlikely to be realistic representations of the Aβ–atrophy relationship. Other methods, designed to model nonlinearity without specifying a parametric form of the curve, such as local regression [18] or smoothing splines [19] have been used in imaging studies to capture nonlinearity in atrophy rates, usually with respect to time or age [20–22]. The increased flexibility of these methods, however, makes the results of the model difficult to summarize and interpret, especially if the goal is to test a formal hypothesis about the shape of a curve that relates Aβ to brain atrophy. A more effective model will adequately capture nonlinearity while remaining interpretable.

One possibility is to allow a separate slope to be estimated during the transition from atrophy rates at low levels of Aβ through to a plateau in rates at highly pathological levels. Such a plateau or saturation point of atrophy with respect to Aβ accumulation will likely vary by region, as will the point at which acceleration begins. We propose a combination of local regression and piecewise-linear splines to capture the variation of atrophy rates across the spectrum of Aβ levels. The model allows three separate slopes to be estimated, one before a potential transition period when changes in Aβ have minimal or no association with atrophy rates, one during the transition and one after. This model is similar to the trilinear model used in Brooks et al. [23], but applied at the population level rather than the individual level. Parameters for changes in the slope of the association of Aβ with atrophy are easily interpreted and tested for statistical significance. An initial step in the model fitting process uses local regression to guide the selection of knot locations, i.e. points at which the slope may change.

We hypothesize that piecewise-linear splines will adequately characterize the relationship between CSF Aβ and regional brain atrophy while identifying and testing for departures from linearity. For regions that demonstrate changes in atrophy rates across the span of CSF Aβ, periods of acceleration and/or saturation will be identified via the selection of spline knot locations. Knot locations will be taken as data-driven estimates of the beginning and ending of the period of transition. The estimation of these transition periods may be important in the optimization of clinical trials for therapies aimed at reducing Aβ-related atrophy.

2. Methods

2.1. Participants

Data were obtained from the ADNI database (adni.loni.usc.edu). ADNI participants were recruited from over 50 sites across the United States and Canada (see www.adni-info.org). The population in this study included ADNI-1 participants who were classified as healthy controls or mild cognitive impairment (MCI) subjects at ADNI screening, who were tested for CSF $A\beta_{42}$, and who had successful longitudinal FreeSurfer processing of MR images.

2.2. CSF biomarker concentrations

A CSF sample was collected at study baseline by lumbar puncture. CSF $A\beta_{42}$ was measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with the Research Use Only INNOBIA AlzBio3 kit (Fujirebio/Innogenetics, Ghent, Belgium) [17,24].