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

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Abstract

Background: 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.

Conclusion: 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 Aβ23 threshold. This implies that signs of brain atrophy develop before the current conventional definition of “preclinical AD”.

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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 Aβ42, 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 Aβ42 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].
2.3. MRI acquisition and processing

At each site, the subjects underwent the standardized 1.5 T MRI protocol of ADNI, as described in Jack et al. [25]. For more detail, see the “MRI acquisition and processing” section of the Supplemental Material, available online.

2.4. Statistical analysis

Baseline associations between CSF Aβ42 and demographic/clinical factors were assessed using Wilcoxon tests for categorical variables (gender, APOE ε4 positivity) and Spearman correlation for continuous variables (age, education, ADAS-cog). Baseline associations were compared within and across diagnostic groups.

Up to 4 years of repeated measures of 47 regional volumes of gray matter were averaged over right and left hemispheres. The estimation of the association between CSF Aβ42 and atrophy in each of the 47 regions, and global atrophy, was done in two steps. In the first step, longitudinal volumes were regressed on time since baseline scan using mixed effects regression. All models included both a random intercept and slope. In a second step, subject-specific slopes from the mixed model were then regressed on baseline CSF Aβ42 level, adjusting for age and gender, using ordinary least squares regression. In the second regression, the effect of CSF Aβ42 was modeled using three line segments, separated by two spline knots to allow for departures from linearity.

To improve the fit of the splines, local regression was used to guide the selection of knot locations. The sparsity of data near the clinical threshold of CSF Aβ42 used to guide the selection of knot locations. The sparsity of the spline models to predict atrophy, as measured by cross-validated R², was similar to the predictive ability of the local regression on CSF Aβ, while allowing knot locations to vary from 125 to 250 ng/L. For each region, locations were chosen to maximize agreement with local regression fits. Models were then refit with splines and selected knot locations.

Steps 1 and 2 were repeated in 500 bootstrap samples to estimate confidence intervals for the association of CSF Aβ42 with atrophy using the 2.5th and 97.5th percentiles. We used the studentized bootstrap [26] with a false discovery rate correction [27] to obtain P-values for slopes and test for significance of acceleration/saturation. All tests were two sided. Likelihood ratio tests and AIC were used to compare the spline vs. dichotomous parameterization of CSF Aβ42. All analyses were done in R v2.12.

3. Results

One hundred and eight controls and 183 MCI subjects had both CSF and longitudinal structural MRI data and were included in the analysis. The median number of scans for both controls and MCI subjects was 5, with 291 scans (baseline), 282 (month 6), 263 (month 12), 143 (month 18, MCI only), 209 (month 24), 143 (month 36), and 35 (month 48). There were no significant associations between baseline CSF Aβ42 and age, gender, or education (Table 1). CSF Aβ42 was significantly associated with both APOE ε4 positivity and ADAS-cog within both diagnostic groups.

Plots of six regions including both MCI and control subjects are shown in Fig. 1. Regions in the plot were selected to show where the trilinear model appeared to fit well (hippocampus, entorhinal cortex, banks of the superior temporal sulcus, and middle temporal gyrus), one region where the spline and local regression differed, and a control region where the association between CSF Aβ42 and atrophy was weak (pericalcarine). Spline, binary, and local regression curves are shown and 95% confidence intervals for the spline curve. The ability of the spline models to predict atrophy, as measured by cross-validated R², was similar to the predictive ability of the local regression models, with most regions differing by <0.01, and 3 of the 47 regions differing by almost 0.02.

Table 2 shows the knot locations, parameter estimates, P-values and false discovery rate (FDR)-corrected P-values for each spline segment, for each region that demonstrated at

<table>
<thead>
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<th>Table 1 Baseline characteristics</th>
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<tr>
<td><strong>Controls (N = 108)</strong></td>
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<tr>
<td>CSF Aβ42, ng/L</td>
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<tr>
<td>Age</td>
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<td>Gender (F)</td>
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<td>Education (yrs)</td>
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<td>APOE ε4+</td>
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Abbreviations: MCI, mild cognitive impairment; CSF, cerebrospinal fluid; SD, standard deviation; Aβ, amyloid beta.

*Spearman correlation with Aβ and corresponding P-value.

Wilcoxon rank sum test for Aβ and corresponding P-value.
least marginal atrophy acceleration associated with Aβ42 ($P < .10$). The parameter estimate for segment one (lowest, most pathological values of CSF Aβ42) is the change in atrophy rate associated with a one unit increase of CSF Aβ42. Note that all $P$-values are nonsignificant for segment one, indicating that there is no association between atrophy and Aβ42 once levels of amyloid have become highly pathological. The estimate for the slope for segment 2 (transition period) is the sum of the estimates for segment 1 and 2. Similarly, the slope for segment 3 is the sum of all three estimates. In other words, for segments 2 and 3, the parameters are estimates of the change in slope, i.e. acceleration or stabilization, relative to the prior segment. A negative parameter estimate for segment 3 indicates an acceleration of atrophy as CSF Aβ42 levels decrease from high levels to the transition period. A positive estimate for segment 2 indicates a stabilization of atrophy rates as subjects move from the transition period to low levels of CSF Aβ42. Twelve regions demonstrated significant stabilization (segment 2 in Table 2), but became only marginally significant after FDR correction. All regions in Table 2 show negative estimates for segment 3 and positive estimates for segment 2.

Models using the binary parameterization of CSF Aβ42 were compared with the spline models using likelihood ratio tests and AIC. The spline model had a lower AIC and was significantly better fitting for the hippocampus ($P = .03$), inferior temporal lobe ($P = .05$), entorhinal cortex ($P = .05$), cuneus ($P < .01$), putamen ($P = .05$), and the brainstem ($P = .05$). The spline model had a lower AIC and showed some evidence of a better fit according to a likelihood ratio test for the parahippocampus, middle temporal gyrus, banks of the superior temporal sulcus (bankssts), thalamus, precentral, postcentral, midposterior corpus callosum, and the central corpus callosum ($P < .10$). The binary form of CSF Aβ42 did not fit any of the regions significantly better than the spline model, although it was a marginally better fit for the precuneus ($P = .10$, smaller AIC for the binary model). None of the other regions differed in fit ($P > .10$).

Fig. 2 shows the ordering of the transition periods with respect to the left-hand, or normal, side of the period. Regions toward the top of the figure begin their transition earlier. A red circle on the left indicates significant acceleration (or stabilization if on the right), $P < .05$. A yellow
circle indicates marginally significant acceleration/stabilization, \( P < .10 \).

In the MCI group alone, the hippocampus, middle temporal gyrus, banks of the superior temporal sulcus, rostral anterior cingulate, cuneus, insula, and brainstem showed marginally significant \( (P < .10) \) acceleration (significant for the hippocampus and middle temporal lobe, \( P < .05 \)), while the hippocampus, banks of the superior temporal sulcus, rostral anterior cingulate, and middle temporal gyrus all showed significant stabilization of rates. The cuneus showed marginally significant stabilization \( (P < .10) \). In controls, the amygdala, cuneus and caudate showed marginally significant points of acceleration. Only the cuneus stabilized with marginal significance (data not shown).

4. Discussion

The findings of this analysis were (1) the trilinear spline model provided significantly improved error reduction compared with the binary parameterization for several brain regions, and in no instance did the binary parameterization provide a significantly better fit than the trilinear spline model, (2) the periods of atrophy acceleration are evident in several regions over the span of CSF \( \mathrm{A}_\beta \) accumulation, (3) the start of these acceleration periods vary by brain region, and (4) trilinear spline modeling demonstrates that some brain regions have accelerated atrophy well before subjects cross the threshold defining amyloid positivity in preclinical AD.

The first finding was that modeling of CSF \( \mathrm{A}_\beta \) via splines results in better fitting models with more predictive accuracy compared with the dichotomous model. The spline model estimates of acceleration and stabilization of atrophy are consistent with local regression estimates, but spline models also provide estimates of transition points. The spline models also appear less prone to overfitting at the boundaries of the data, i.e. the amygdala in Fig. 1. The increased predictive ability of the trilinear model over the dichotomous model was most clearly seen in regions in the temporal and parietal lobes where transition periods were most significant.

Aside from a methodological improvement in statistical modeling, the important biological finding of this work is that regions with distinct periods of accelerated volume loss show signs of atrophy well before the CSF \( \mathrm{A}_\beta \) greater than 192 ng/L threshold. That is, subjects with CSF \( \mathrm{A}_\beta \) greater than 192 ng/L are not considered to have “preclinical AD” by current convention. Nevertheless, the results in Fig. 2 clearly show that the insula, most of the temporal lobe, and much of the parietal lobe fit the profile for a sigmoid-like curve with the evidence of acceleration starting at CSF \( \mathrm{A}_\beta \) levels between 210 and 225 ng/L. The stabilization of rates appears to begin near CSF \( \mathrm{A}_\beta \) 130 ng/L for most temporal lobe regions. When using a dichotomous model, subjects approaching the threshold for \( \mathrm{A}_\beta \) positivity are included in the \( \mathrm{A}_\beta \) negative group, whereas the trilinear model demonstrates that they are transitioning to \( \mathrm{A}_\beta + \).

Combining these transitioning subjects with subjects who will remain \( \mathrm{A}_\beta - \) biases the association of \( \mathrm{A}_\beta \) with the response in the \( \mathrm{A}_\beta - \) group toward the \( \mathrm{A}_\beta + \) group, reducing group differences and the power to detect the effect of \( \mathrm{A}_\beta \) on other aspects of AD pathology, including brain atrophy. Further categorization of subjects into incident \( \mathrm{A}_\beta + \) or transitioning \( \mathrm{A}_\beta \) groups can be seen in recent research [28,29].
The finding of early Aβ-related atrophy in temporal and parietal lobes and the cingulate gyrus agrees with previous reports [8–12]. Several regions, including the insula, posterior cingulate, amygdala, putamen, and precuneus show early signs of atrophy even though they do not reach the magnitude of atrophy seen in much of the temporal lobe during the course of dementia due to AD. Fig. 2 shows that these regions may show signs of Aβ related atrophy before the hippocampus and entorhinal cortex which are generally thought to show neurodegeneration very early in AD. The length of the transition period with respect to Aβ is similar among the temporal lobe regions, but appears shorter in many of the parietal regions (Fig. 2). This extended acceleration period in the temporal lobe may contribute to atrophy rates reaching much higher levels compared with other lobes in the progression of AD, despite the possibility that brain atrophy may start to accelerate earlier in nontemporal regions.

Not all regions show a pattern of stability before a distinct transition period. In MCI subjects, there is a linear decline in the amygdala until an ostensible stabilization period near CSF Aβ42 = 125 ng/L. If a point of acceleration exists for MCI subjects in the amygdala, it may have occurred beyond the upper range of CSF Aβ42 in these subjects, suggesting an early effect of Aβ on atrophy in the amygdala. A similar pattern occurred in the fusiform and parahippocampus of MCI subjects.

Control subjects do not have as steep a transition from high levels of CSF Aβ42 to low levels even though a substantial number of control subjects are well beyond the clinical threshold for Aβ positivity. This suggests that an excess accumulation of Aβ alone does not necessarily result in an immediate increase in rates of atrophy and cognitive impairment. Latent factors, absent in controls, may contribute to an increased vulnerability of MCI subjects to the effects of Aβ. For example, the duration of exposure to Aβ pathology may be important for effects on brain atrophy, and may differ between controls and MCI. Commonly occurring copathologies such as Lewy Body (LB) and transactive response DNA binding protein 43 (TDP-43) pathology and cerebrovascular disease (CVD) may also influence the association of Aβ at any stage of preclinical or prodromal AD and will likely need to be taken into account and demonstrated in other cohorts [30–32].

One important implication for clinical trials attempting to treat Aβ-related atrophy and subsequent cognitive decline may be the recruitment of subjects with low enough levels of Aβ pathology for a drug to successfully change the course of Alzheimer's Disease.
of disease, but high enough for a placebo group to demonstrate an increased rate of atrophy, while also screening out subjects with LB, TDP-43 inclusions, or CVD to avoid confounds linked to these other pathologies when interpreting the response of individuals to a therapy that only targets Aβ pathology.

One limiting factor of this analysis is the sparsity of CSF Aβ42 data near the previously established clinical threshold 192 ng/L, precisely the interval of most interest. This sparsity will likely have some effect on the knot location selection, parameter estimates, and the power to detect significant acceleration in atrophy rate. By using CSF to measure Aβ pathology, we did not have information about sites of Aβ accumulation and could not account for variation in spatial deposition, another complicating factor likely to affect regional atrophy. Also, we report significant and marginally significant results. Marginally significant results should be interpreted with caution given the large number of regions tested, however, the common direction of the slopes across all AD-implicated regions provides some evidence of a more mild association rather than type I error.

In conclusion, we show that the relationship between CSF Aβ42 and regional brain atrophy rates may be parameterized by trilinear functions, providing an improved model of their association and may improve the characterization of Aβ pathology, compared with the usual binary classification. The results are consistent with the view that signs of brain atrophy develop before the decrease of CSF Aβ42 required in the current conventional definition of “preclinical AD”.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jaldz.2014.11.002.
RESEARCH IN CONTEXT

1. Systematic review: To identify all relevant research in the literature pertaining to our topic, we searched for papers referencing structural imaging in Alzheimer’s disease and mild cognitive impairment, amyloid imaging, cerebrospinal fluid (CSF) biomarkers, brain atrophy, and statistical methods applied to longitudinal imaging studies including nonlinear and local regression, splines, trilinear models, and mixed-effects regression. Our authors, with expertise in imaging, CSF biomarkers, and statistics, reviewed and added to the citations to ensure completeness.

2. Interpretation: Our results demonstrate a statistical method that improves the characterization of the relationship between amyloid beta (Aβ) and atrophy compared with the most commonly used method in the literature. Our method is more powerful and offers a temporal ordering of the acceleration of atrophy of individual brain regions. This information will help facilitate the design of clinical trials aimed at treating amyloid pathology.

3. Future directions: Studies focused on subjects transitioning from Aβ negative to Aβ positive in a longitudinal setting will be required to more precisely estimate the evolution of regional atrophy.

References


