Predicting Reduction of Cerebrospinal Fluid β-Amyloid 42 in Cognitively Healthy Controls

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Alzheimer disease (AD) is believed to have a long preclinical stage characterized by β-amyloid (Aβ) accumulation without symptoms. Several trials focus on this stage and use biomarkers to include Aβ-positive participants, but an even earlier prevention of Aβ accumulation may be an effective treatment strategy.

OBJECTIVE To determine whether people who appear to be Aβ negative but are at high risk for Aβ positivity within the near future can be identified.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal biomarker cohort study involving 35 cognitively healthy individuals who underwent cerebrospinal fluid (CSF) sampling for up to 3 years during the study (October 24, 2005, to September 1, 2014). All participants had normal CSF Aβ42 levels at baseline.

MAIN OUTCOMES AND MEASURES Predictors of future Aβ positivity (levels of CSF Aβ42 declining below a previously validated cutoff level of 192 ng/L) tested by random forest models. Tested predictors included levels of protein in the CSF, hippocampal volume, genetics, demographics, and cognitive scores.

RESULTS The CSF Aβ42 levels declined in 11 participants, and the CSF became Aβ positive. The baseline CSF Aβ42 level was a strong predictor of future positivity (accuracy, 79% [95% CI, 70%-87%]). Ten of 11 decliners had baseline CSF Aβ42 levels in the lower tertile of the reference range (<225 ng/L), and 22 of 24 nondecliners had baseline CSF Aβ42 levels in the upper 2 tertiles (≥225 ng/L). A high CSF P-tau level was associated with decline (accuracy, 68%; 95% CI, 55%-81%).

CONCLUSIONS AND RELEVANCE Baseline CSF Aβ42 levels in the lower part of the reference range are strongly associated with future Aβ positivity. This finding can be used in trials on very early prevention of Alzheimer disease to identify people at high risk for Aβ accumulation as defined by low CSF Aβ42 levels.

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accretion. We therefore tested the hypothesis that baseline CSF Aβ42, biomarkers of neurodegeneration, demographic factors, and cognitive scores could be used to identify people at risk for Aβ accumulation as determined by low CSF Aβ42 levels, within 3 years.

Methods

Study Design

Data used in the preparation of this article were obtained from the Alzheimer Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year, public-private partnership. The principal investigator of this initiative is Michael W. Weiner, MD, Veterans Affairs Medical Center and University of California, San Francisco. The 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 the ADNI was to recruit 800 individuals, but the ADNI has been followed by ADNI-Grand Opportunity (ADNI-GO) and ADNI-2. To date, these 3 protocols have enrolled more than 1500 adults aged 55 to 90 years to participate in the research, consisting of cognitively normal older individuals, people with early or late mild cognitive impairment, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-GO, and ADNI-2. Individuals originally recruited for ADNI-1 and ADNI-GO had the option to be monitored in ADNI-2.9 The present study was conducted from October 24, 2005, to September 1, 2014. Institutional review board approval was received at all involved sites. Written informed consent was obtained from all participants.

Cohort

Our study population consisted of cognitively healthy individuals serving as controls enrolled in ADNI-1 or ADNI-2. Inclusion and exclusion criteria have been described in detail.9 Briefly, all control participants included in ADNI were between the ages of 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, were free of any significant neurologic disease, had a Mini-Mental State Examination10 score of 24 or higher, and had a Clinical Dementia Rating scale11 score of 0. For the present study, we only included those with available longitudinal data on CSF Aβ42 levels and baseline CSF Aβ42 levels indicating a lack of Aβ accumulation at baseline as determined by a validated cutoff level (192 ng/L).

CSF Biomarkers

All participants underwent CSF sampling at baseline and at least once (yearly or every second year) in a follow-up visit during 3 years (or shorter in 5 individuals who became Aβ positive during follow-up). Measurement of levels of Aβ42, T-tau, and P-tau was performed using the multiplex xMAP Luminex platform (Luminex Corp) with the INNO-BIA AlzBio3 kit (Innogenetics) as described previously.5,12 Longitudinal samples for each participant were analyzed on the same plate in the same analytical run.13 Within-run coefficients of variation were 6.5% or less. Parts of the longitudinal data have been published.13

Cognition

The Alzheimer Disease Assessment Scale-Cognitive Subscale, version 11 (ADAS-cog11),14 logical memory delayed recall, Rey Auditory Verbal Learning Test (AVLT) delayed recall,15 and Trail Making Test, part B (Trail B)16 were performed at baseline. For analysis of longitudinal cognitive scores, we used up to 8 years of follow-up data.

Structural Magnetic Resonance Imaging

Brain scans using T1-weighted structural magnetic resonance imaging (MRI) were acquired at baseline with 1.5-T (ADNI-1) or 3-T (ADNI-2) MRI scanners using a sagittal volumetric magnetization-prepared rapid gradient echo nonaccelerated sequence.17 Quantification was done in an automated pipeline using FreeSurfer (version 4.3 for ADNI-1 and version 5.1 for ADNI-2, http://surfer.nmr.mgh.harvard.edu/fswiki).18,19 Individuals whose quality control test results were below standard were excluded. Data on hippocampal volume (mean of right and left) were used. Hippocampal volume was adjusted for total intracranial volume. Because the acquisition and processing of images differed between ADNI-1 and ADNI-2, the data from these study groups were analyzed separately. Individuals with an adjusted hippocampal volume below the 25th percentile within each study group were labeled as having small hippocampal volume. The choice of the 25th percentile was a trade-off between achieving adequate group sizes and a level of hippocampal volume that may be associated with early-stage brain injury.

PET Imaging

We included data on ADNI-1 participants who had undergone carbon 11(11C)–labeled Pittsburgh compound B PET scanning and ADNI-2 participants who had undergone florbetapir F 18 PET scanning to test for the presence of brain Aβ accumulation as estimated by PET (using previously established cutoffs for 11C-Pittsburgh compound B, 1.47 standardized uptake volume ratio [SUVR],20 and 18F-florbetapir, 1.11 SUVR21-23).

Statistical Analysis

Baseline biomarkers (levels of CSF Aβ42, CSF T-tau, and CSF P-tau and small hippocampal volume), demographic factors (age, sex, and educational level), genetics (presence of APOE ε4 and APOE ε2 alleles), and cognitive scores (ADAS-cog11, AVLT, Trail B, and logical memory delayed recall) were compared between participants with vs without CSF Aβ42 (termed decliners and nondecliners, respectively) using Mann-Whitney tests and χ² tests. Longitudinal cognition was examined by linear mixed-effects models adjusted for age, sex, and educational level.

The binary classification of CSF Aβ42 decline vs nondecline was the dependent variable in random forest analyses.
We classified participants as CSF Aβ42 decliners if the observed CSF Aβ42 level became lower than 192 ng/L within 3 years. Those whose Aβ42 level remained negative at 3 years were classified as nondecliners. Ten individuals lacked data at exactly 3 years but had data available at 4 years, 5 years, or both. These participants were classified as nondecliners if the 4- to 5-year follow-up sample was negative (n = 9) and as decliners if both the 2- and 4-year follow-up samples were positive (n = 1). No participants had the potentially ambiguous combination of a negative 2-year sample and a positive 4-year sample; one person in the original data set had samples at baseline, 1 year (negative), and 6 years (positive) and was excluded from all analyses because his status at 3 years was ambiguous. Figure 1 shows the observed CSF Aβ42 data, and the Table presents the demographics and baseline biomarker data and cognitive scores. The only significant difference between decliners and nondecliners was the lower baseline CSF Aβ42 levels in the decliners. There were no significant differences between the CSF Aβ42 groups in longitudinal trajectories of cognitive scores (P > .05).

Predicting CSF Aβ42 Decline
We performed random forest analyses with decliners vs nondecliners as the dependent variable and demographic factors, baseline biomarker data, and cognitive scores as predictors. The results are presented as OOB in the Table and as ROC curves for continuous predictors in Figure 2 (receiver operating characteristic curves are not meaningful for dichotomous predictors). Baseline CSF Aβ42 level was the strongest individual predictor of future decline (OOB accuracy, 79%; 95% CI, 70%-87%). The high diagnostic accuracy for baseline CSF Aβ42 was in agreement with the distribution of baseline CSF Aβ42 level in decliners and nondecliners (Figure 1 and the Table). The individual decision trees for CSF Aβ42 favored splits at a level corresponding to the lower tertile of baseline CSF Aβ42 (225 ng/L). Among the 12 participants with baseline CSF Aβ42 levels less than 225 ng/L, 10 were decliners (positive predictive value, 83%). Among the 23 participants with baseline CSF Aβ42 levels of 225 ng/L or more, 22 were nondecliners (negative predictive value, 96%).

Baseline CSF P-tau levels also significantly predicted future decline (OOB accuracy, 68% [95% CI, 55%-81%]). The individual decision trees for CSF P-tau favored splits at CSF P-tau 25 ng/L, which was close to the upper tertile of baseline CSF P-tau (26 ng/L) and also close to a previously suggested cutoff for CSF P-tau to identify AD (23 ng/L, when analyzed at the same laboratory and with the same assays as in the ADNI study25). Among the 10 participants with baseline CSF P-tau levels higher than 25 ng/L, 6 were decliners (positive predictive value, 60%). Among the 25 individuals with baseline CSF P-tau levels less than 25 ng/L, 20 were nondecliners (negative predictive value, 80%).

Sex, APOE ε2, APOE ε4, and small hippocampal volume also appeared to be significant individual predictors (OOB accuracy, 64%-69%) (Table). However, closer inspection of these random forest models revealed that the models classified all but one participant as nondecliners, and their OOB accuracy therefore corresponds to the percentage of nondecliners in the examined population.

We performed additional random forest analyses testing a combination of CSF Aβ42 and P-tau, which had an OOB accuracy rate of 84% (95% CI, 72%-97%). We also tried combinations of CSF Aβ42, P-tau, and other predictors. The best accuracy was seen for a combination of CSF Aβ42, P-tau, and the
Predicting Reduction of CSF β-Amyloid 42

Original Investigation Research

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findings. therewasnochangeintheoneparticipantwithPET-positive cliners and 2 nondecliners; none became PET positive, and dataduringthestudyperiodwereavailablefor6CSFAβ42de-

wasinitiallyderivedfromasampleofpatientswithautopsy-to become Aβ positive during follow-up. The 192 ng/L cutoff  
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dictorofdecliningCSFAβ42.IndividualswithCSFAβ42lev-

thresholdof192ng/L. BaselineCSFAβ42levelwasastrongpre-

finedastheCSFAβ42levelfallingbelowtheapriori–defined  
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was the CSF Aβ42 level falling below the a priori–defined  
threshold of 192 ng/L. Baseline CSF Aβ42 level was a strong  
predictor of declining CSF Aβ42. Individuals with CSF Aβ42  
levels in the lower tertile of the reference range were very  
likely to become Aβ positive during follow-up. The 192 ng/L  
cutoff was initially derived from a sample of patients with autopsy- 
confirmed AD dementia vs nonautopsy–confirmed controls.5  
This threshold, and corresponding thresholds used for Aβ PET  
imaging, may be too stringent to detect very early pathology.  
The findings of our study suggest that a more liberal (higher)  
cutoff level could be explored in cognitively healthy controls.

The recent failures of anti-amyloid drug trials, such as the  
phase 3 trials of bapineuzumab29 and solanezumab,30 have  
been blamed partly on the fact that some of the participants  
did not have Aβ accumulation.31 In addition, the disease may  
drive itself toward some point.32 This theory is  
contradictsthishypothesisandsuggeststhatalownormalCSF  
peptide. Thus, CSF Aβ42 levels in the low normal range could  
be due to a physiologically low Aβ production rate, which  
may not be associated with further decline. However, our  
finding contradicts this hypothesis and suggests that a low  
normal CSF Aβ42 level is rarely a benign phenomenon since  
it is strongly  
associated with future Aβ decline. The finding agrees  
with previous results using Aβ PET, in which cognitively healthy  
people who became Aβ positive during follow-up had a higher  
baseline Aβ signal than people who remained Aβ negative.27  
which implies an association between Aβ PET levels that are  
out-of-bag accuracies (ranging from 0 to 1, where 1 is perfect  
accuracy) are from random forest analyses. Seven APOE ε2–positive  
participants had 1 APOE ε2 and 1 APOE ε3 allele. Three APOE  
ε4–positive participants had 1 APOE ε4 and 1 APOE ε3 allele and one  
individual had 1 APOE ε2 allele. For sex, APOE, and small  
hippocampus, the out-of-bag accuracy appears to  
be significant, but closer inspection of these models showed that  
they classified all cases (or all but 1 case) as nondecliners,  
and these accuracies therefore represent the  
frequency of nondecliners in the population.

Information was missing on 1 participant.

Comparison with Aβ PET
Eight participants had Aβ PET data at the start of the study (5  
at baseline and 3 at the 1-year follow-up). One of these  
individuals was PET positive (18F-florbetapir SUVR, 1.21; CSF Aβ42,  
201 ng/L at baseline and 182 ng/L at follow-up). Follow-up PET  
data during the study period were available for 6 CSF Aβ42  
decliners and 2 nondecliners; none became PET positive, and  
there was no change in the one participant with PET-positive  
findings.

Discussion
The main finding of this study was that it is possible to predict  
declining levels of CSF Aβ42 in cognitively healthy individu-

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Table. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 35)</th>
<th>CSF Aβ42 Decliners (n = 11)</th>
<th>CSF Aβ42 Nondecliners (n = 24)</th>
<th>P Valuea</th>
<th>Out-of-Bag Accuracy (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.1 (6.0)</td>
<td>76.0 (5.8)</td>
<td>76.1 (6.2)</td>
<td>.96</td>
<td>0.45 (0.32-0.58)</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.7 (3.0)</td>
<td>16.0 (2.6)</td>
<td>15.5 (3.3)</td>
<td>.86</td>
<td>0.56 (0.45-0.68)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (49)</td>
<td>4 (36)</td>
<td>13 (54)</td>
<td>.54</td>
<td>0.69 (0.65-0.72)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (51)</td>
<td>7 (64)</td>
<td>11 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE ε2, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (20)</td>
<td>1 (9)</td>
<td>6 (25)</td>
<td>.52</td>
<td>0.64 (0.57-0.71)</td>
</tr>
<tr>
<td>Negative</td>
<td>28 (80)</td>
<td>10 (90)</td>
<td>18 (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE ε4, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4 (11)</td>
<td>2 (18)</td>
<td>2 (8)</td>
<td>.78</td>
<td>0.69 (0.65-0.72)</td>
</tr>
<tr>
<td>Negative</td>
<td>31 (89)</td>
<td>9 (82)</td>
<td>22 (92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>5.0 (2.3)</td>
<td>5.6 (2.8)</td>
<td>4.7 (2.0)</td>
<td>.35</td>
<td>0.59 (0.44-0.73)</td>
</tr>
<tr>
<td>Trail B</td>
<td>79.6 (24.7)</td>
<td>87.3 (31.8)</td>
<td>76.1 (20.6)</td>
<td>.34</td>
<td>0.54 (0.40-0.68)</td>
</tr>
<tr>
<td>Logical memory delayed recall</td>
<td>12.8 (3.8)</td>
<td>12.8 (3.3)</td>
<td>12.8 (4.0)</td>
<td>.89</td>
<td>0.58 (0.36-0.80)</td>
</tr>
<tr>
<td>AVLT delayed recall</td>
<td>8.5 (3.0)</td>
<td>7.6 (2.9)</td>
<td>9.0 (2.9)</td>
<td>.11</td>
<td>0.56 (0.39-0.73)</td>
</tr>
<tr>
<td>Baseline biomarkers</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CSF Aβ42, ng/L</td>
<td>242 (31)</td>
<td>211 (12)</td>
<td>257 (25)</td>
<td>&lt;.001</td>
<td>0.79 (0.70-0.87)</td>
</tr>
<tr>
<td>CSF T-tau, ng/L</td>
<td>63 (21)</td>
<td>71 (25)</td>
<td>59 (18)</td>
<td>.15</td>
<td>0.45 (0.35-0.55)</td>
</tr>
<tr>
<td>CSF P-tau, ng/L</td>
<td>23 (7.9)</td>
<td>25 (7.9)</td>
<td>21 (7.8)</td>
<td>.16</td>
<td>0.68 (0.55-0.81)</td>
</tr>
<tr>
<td>Small hippocampus, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True</td>
<td>10 (29)</td>
<td>3 (27)</td>
<td>7 (29)</td>
<td>&gt;.99</td>
<td>0.68 (0.65-0.71)</td>
</tr>
<tr>
<td>False</td>
<td>24 (69)</td>
<td>8 (73)</td>
<td>16 (67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; ADAS-cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; AVLT, Auditory Verbal Learning Test; CSF, cerebrospinal fluid; Trail B, Trail Making Test, part B.

a P values are for comparisons between emerging Aβ accumulation (decliners) and the nonDECLiners (Mann-Whitney tests and χ2 tests).
b Out-of-bag accuracies (ranging from 0 to 1, where 1 is perfect accuracy) are from random forest analyses. Seven APOE ε2–positive participants had 1 APOE ε2 and 1 APOE ε3 allele. Three APOE ε4–positive participants had 1 APOE ε4 and 1 APOE ε3 allele and one individual had 1 APOE ε2 allele. For sex, APOE, and small hippocampus, the out-of-bag accuracy appears to be significant, but closer inspection of these models showed that they classified all cases (or all but 1 case) as nondecliners, and these accuracies therefore represent the frequency of nondecliners in the population.

Information was missing on 1 participant.

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supported by some of the autopsy data from the AN1792 trial,33 in which amyloid immunization may have removed amyloid plaques without affecting the course of the disease. Several new trials therefore use Aβ biomarkers to verify that participants have amyloid accumulation, both for tertiary and secondary prevention, and/or focus on patients with less severe clinical disease.34,35 These results suggest that an even earlier prevention—before Aβ biomarkers have reached the cutoff normally associated with widespread pathology—could also be an attractive approach since there are several problems associated with treatment when pathology is established. For example, successful prevention in people with established amyloid accumulation may be hampered by a large variability in the length of time that individuals have been exposed to the toxic effects of amyloid. Some people may have become amyloid positive very recently and others may have had amyloid depositions for years, putting them at higher risk for imminent spread of tau pathology and cognitive impairment. However, the benefits of primary prevention must be weighed against possible risks, costs, and the availability of early screening and intervention.

There has been discussion about whether Aβ or neurodegeneration appears first during the course of AD.7,8,27 Although the present study was not specifically aimed at answering this question, our results suggest that signs of Aβ accumulation and signs of tau-related neurodegeneration may appear early in the disease process since a high baseline CSF P-tau level was also a significant predictor of future Aβ level decline. Complicating analyses of preclinical Aβ and neurodegeneration, brain Aβ may have very early effects on neurodegeneration, even before Aβ biomarkers become clearly positive.36 The ADNI investigators37 recently found that hippocampal atrophy rates started to accelerate at CSF Aβ42 levels of approximately 220 ng/L,37 which was about the same level of CSF Aβ42 that was associated with a high risk of declining CSF Aβ42 in the present study. Together, these findings suggest that the emergence of Aβ accumulation and neurodegeneration is coupled even early (from a clinical perspective) in the disease process. Of course, these conclusions are based on currently available biomarker tools. For example, CSF Aβ42 may lack sensitivity for the most toxic forms of brain amyloid.

This study has several limitations. The main limitation is the small sample size, especially of CSF Aβ42 decliners, which restricts our power to identify significant predictors. The results therefore need to be confirmed in larger studies. Furthermore, the participants had a mean age of 76 years, and primary prevention of Aβ accumulation should be explored in younger individuals given the long duration of preclinical amyloid accumulation.38,39 The study group included few APOE ε4 carriers since most elderly APOE ε4 carriers are CSF Aβ42 positive at baseline. Thus, our results may not be generalizable to APOE ε4 carriers. Another possible limitation is the inclusion of individuals who were close to the cutoff level at baseline, which may lead to a bias by those crossing the threshold on the basis of random variation. However, the decliners decreased by a mean (SD) of 14.2% (5.9%) in CSF Aβ42 levels from baseline to their last measurement, which clearly exceeded the intra-assay variability for CSF Aβ42 (coefficient of variation, ±6.5%35-37). In contrast, although some participants who were classified as nondecliners had negative slopes, the mean (SD) change in the nondecliner group was within the intra-assay variability (±5.3% [9.5%]). This argues against random variation having a major effect on the classification of the participants. The fact that individuals who were classified as decliners had both lower baseline values and steeper decline of CSF Aβ42 levels than did those who were classified as nondecliners supports the idea that CSF Aβ42 levels may have a sigmoidal trajectory, as previously suggested.40 Our definition of decliners did not include people whose CSF Aβ42 level decreased without reaching the cutoff value (192 ng/L) within 3 years. Although some of those individuals may be moving toward Aβ accumulation, excluding them from the decliner group reflects possible procedures in future trials aimed at preventing Aβ accumulation. We only analyzed hippocampal volume as a predictor of future CSF Aβ42 level decline, but future studies may also explore other structures, including the precuneus, entorhinal, lateral temporal, and lateral parietal cortices. Likewise, several other cognitive tests could be explored. Recently, a composite score for secondary prevention AD trials was presented (Alzheimer’s Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite).41 However, the ADNI procedures allow only an approximation of this score, and the effects of baseline Aβ level on the score were very mild in ADNI controls42; therefore, we did not include the score in the present study. Finally, we could not confirm Aβ accumulation with an independent technology. Few participants in this group underwent PET Aβ imaging, and there was no evidence of PET Aβ positivity in the CSF Aβ42 decliners. This is difficult to interpret given the small number of people with PET imaging results available, but previous reports42-43 have suggested that CSF Aβ42 levels may be reduced before PET Aβ posi-
predictivity is observed. Therefore, a longer follow-up period would be necessary to determine PET evidence of Aβ accumulation in this group.

Conclusions

Our study shows that it is possible to identify individuals at risk for Aβ accumulation. Such people are primarily characterized by CSF Aβ42 levels slightly above the cutoff level of 192 ng/L. This finding is in agreement with a previously proposed model of sigmoidal Aβ biomarker trajectories,\(^2\) as well as with findings using Aβ PET,\(^2\) and adds to a previous determination that CSF proteins may be used to predict longitudinal reduction of CSF Aβ42.\(^4\) Individuals with CSF Aβ42 levels in the low reference range may be optimal candidates for early intervention trials aimed at thwarting further Aβ accumulation.

References


Additional information

ARTICLE INFORMATION

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Author Contributions: Dr Mattsson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mattsson, Insel. Acquisition, analysis, or interpretation of data: All authors.

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