**Accuracy of Brain Amyloid Detection in Clinical Practice Using Cerebrospinal Fluid β-Amyloid 42**

A Cross-Validation Study Against Amyloid Positron Emission Tomography

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**IMPORTANCE** Before adding cerebrospinal fluid (CSF) biomarkers to the diagnostic workup of Alzheimer disease, it needs to be determined whether CSF biomarkers analyzed in routine clinical practice can reliably predict cortical β-amyloid (Aβ) deposition.

**OBJECTIVES** To study whether CSF biomarkers, analyzed consecutively in routine clinical practice during 2 years, can predict cortical Aβ deposition and to establish a threshold for Aβ42 abnormality.

**DESIGN, SETTING, AND PARTICIPANTS** This cross-sectional study (The Swedish BioFINDER [Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably] Study) was conducted at 3 memory clinics. It involved consecutively referred, nondemented patients with mild cognitive symptoms (original cohort, n = 118; validation cohort, n = 38).

**EXPOSURES** Amyloid positron emission tomography imaging with 18F-flutemetamol.

**MAIN OUTCOMES AND MEASURES** Analyses of CSF Aβ42, total tau, and phosphorylated tau using an enzyme-linked immunosorbent assay (INNOTEST) in clinical samples.

**RESULTS** The agreement between Aβ classification with CSF Aβ42 and 18F-flutemetamol positron emission tomography was very high (κ = 0.85). Of all the cases, 92% were classified identically using an Aβ42 cutoff of 647 pg/mL or less. Cerebrospinal fluid Aβ42 predicted abnormal cortical Aβ deposition accurately (odds ratio, 165; 95% CI, 39-693; area under the receiver operating characteristic curve, 0.94; 95% CI, 0.88-0.97). The association was independent of age, sex, APOE (apolipoprotein E) genotype, hippocampal volume, memory, and global cognition (adjusted odds ratio, 169; 95% CI, 25-1143). Using ratios of CSF Aβ42:tau or Aβ42:phosphorylated tau did not improve the prediction of Aβ deposition. Cerebrospinal fluid Aβ42 correlated significantly with Aβ deposition in all cortical regions. The highest correlations were in regions with high 18F-flutemetamol retention (eg, posterior cingulum and precuneus, r = −0.72). 18F-flutemetamol retention, but not CSF Aβ42, correlated significantly with global cognition (r = −0.32), memory function (r = −0.28), and hippocampal volume (r = −0.36) among those with abnormal Aβ deposition. Finally, the CSF Aβ42 cutoff derived from the original cohort (≥647 pg/mL) had an equally high agreement (95%; κ = 0.89) with 18F-flutemetamol positron emission tomography in the validation cohort.

**CONCLUSIONS AND RELEVANCE** Cerebrospinal fluid Aβ42 analyzed consecutively in routine clinical practice at an accredited laboratory can be used with high accuracy to determine whether a patient has normal or increased cortical Aβ deposition and so can be valuable for the early diagnosis of Alzheimer disease. Abnormal 18F-flutemetamol retention levels correlate with disease stage in patients with mild cognitive symptoms, but this is not the case for CSF Aβ42 measurements.

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Alzheimer disease (AD) is incurable but there are ongoing trials testing putative disease-modifying drug candidates, most of which target β-amyloid (Aβ). The current consensus is that a future disease-modifying drug will need to be initiated at a preclinical or prodromal stage if it is to demonstrate clinically relevant neuroprotection.6 Given this, an important research area has been to establish diagnostic tools that identify AD pathology at an early stage.7 The hypothetical model detailing the temporal evolution of AD biomarkers by Jack and colleagues5 suggested that the earliest biomarker changes are related to the accumulation of Aβ in the brain. A common clinical way of detecting increased brain Aβ is by measuring the levels of the 42-amino acid isoform of Aβ (Aβ42) in cerebrospinal fluid (CSF). Reduced CSF Aβ42 can alone, or in combination with increased CSF total tau and tau phosphorylated at Thr181 (P-tau), predict progression to AD in patients with mild cognitive impairment (MCI) and healthy elderly individuals with high accuracy up to 10 years before the onset of dementia.4-7 Cerebrospinal fluid analysis of Aβ42 levels is readily available clinically in many countries and is inexpensive. Variations in these measurements are often seen within laboratories over time, precluding clinical use, if appropriate internal and external quality-control systems are not in place.8 To our knowledge, it has not been studied whether levels of CSF Aβ42 can be used with high validity and reliability to detect abnormal brain Aβ deposition when analyzed consecutively over several years in routine clinical practice. Such studies are needed before widespread use of CSF biomarkers in the clinical workup of early AD diagnosis.

Cortical Aβ deposition can be determined directly with positron emission tomography (PET). Several amyloid PET tracers (eg, 18F-flutemetamol) have been approved by the US Food and Drug Administration for the detection of brain Aβ plaque load and have been validated against histopathologic findings with high agreement.9-13 Considering the accessibility of CSF analysis and the robust validation of amyloid PET imaging, it would be advantageous if an abnormal amyloid PET scan finding could be predicted using routine CSF analysis in clinics where PET is not readily available. Several studies have investigated the agreement between CSF Aβ42 measurements and amyloid PET imaging.14-22 These studies have generally shown there is a good correlation between finding low CSF Aβ42 levels and increased amyloid visualized with either 18F-flutemetamol PET or 18F-florbetapir PET. To our knowledge, it has not been studied whether CSF Aβ42 levels correlate with accumulation of Aβ deposition in specific brain regions, except in small populations.16,19,21 Importantly, no previous study has compared CSF Aβ42 levels, consecutively analyzed in routine clinical practice, with amyloid PET imaging to determine whether CSF biomarkers can reliably distinguish amyloid-positive from amyloid-negative individuals. Moreover, to our knowledge, it has not been studied whether CSF biomarkers can predict abnormal Aβ deposition in a clinically heterogeneous cohort with either subjective or objective cognitive symptoms. Therefore, the aims of this study were to (1) investigate the reliability and validity of CSF analyses of Aβ42, tau, and P-tau levels conducted over 2 years in routine clinical assessment using the presence of cortical Aβ deposition detected with 18F-flutemetamol PET as the standard of truth; (2) provide a threshold for CSF Aβ42 reductions that can predict cortical Aβ deposition in a clinically relevant and heterogeneous population of nondemented patients with cognitive symptoms and test this threshold in a second validation cohort; and (3) examine whether CSF biomarkers are related to Aβ deposition in specific regions of the brain.

Methods

Study Population

The study population was part of the prospective and longitudinal Swedish BioFINDER (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably) Study (more study information will be available at www.biofinder.se). The patients were enrolled consecutively at 3 memory outpatient clinics in Sweden. They were referred for assessment of their cognitive symptoms and were included between May 2011 and May 2013. They were thoroughly assessed by physicians with special interest in dementia disorders. The inclusion criteria were that patients (1) were referred to the memory clinics because of cognitive impairment; (2) did not fulfill the criteria for dementia; (3) had a Mini-Mental State Examination (MMSE) score of 24 to 30 points23; (4) were aged 60 to 80 years; and (5) were fluent in Swedish. The exclusion criteria were (1) cognitive impairment that without doubt could be explained by another condition (other than prodromal dementia); (2) severe somatic disease; and (3) refusing lumbar puncture or neuropsychological investigation. These criteria resulted in a clinically relevant population where 79 patients (51%) were classified as having subjective cognitive decline, 58 (37%) as having amnestic MCI, and 19 (12%) as having nonamnestic MCI. The classification was based on a neuropsychological battery assessing the cognitive domains of verbal ability, visuospatial construction, episodic memory, and executive functions, as well as the clinical assessment of a senior neuropsychologist (S.V.). All patients who had undergone a lumbar puncture and a PET scan before June 30, 2013, were included in the original cohort (n = 118) and patients with PET scans performed on or after June 30, 2013, were included in the validation cohort (n = 38). Only the baseline examinations were used for the analyses. The Regional Ethics Committee in Lund, Sweden, approved the study design. All patients gave their written informed consent.

CSF Collection and Analysis

The CSF samples were collected at the 3 centers over 2 years according to standard procedures.2 The CSF was analyzed continuously as part of routine clinical practice; consequently, the CSF samples were analyzed sample by sample and not in batches. The personnel analyzing the CSF samples were not aware that the samples were part of a research study and were thus blinded to the amyloid PET results. The samples were analyzed using commercially available enzyme-linked immunosorbent assays (INNOTEST, Innogenetics) to determine the levels of total tau, Aβ42, and P-tau. More details about the CSF procedures can be found in Table 1 and the Supplement (eAppendix 1).
Table 1. Procedures Used With the Aim to Maintain Long-term Stability for Alzheimer Disease CSF Biomarkers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Procedures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preanalytical factors</td>
<td>Use specific polypropylene tubes for LP and aliquotation; discard the first milliliter of CSF and change to a new tube, if there is a visual blood contamination (CSF tap hemorrhage); follow a standardized procedure for LP (eg, make LP at the same time of the day) and sample handling (eg, centrifugation before aliquotation) at the clinic (for details, see Blennow et al²). CSF can be transported to the laboratory either at RT (if shipment time is &lt; 1 d) or frozen (with dry ice); at the laboratory, unfrozen CSFs are frozen (&gt; 1 d) and frozen CSFs are kept frozen so that all samples go through exactly 1 freeze/thaw cycle prior to analysis (for more details regarding preanalytical procedures, see Blennow et al²).</td>
</tr>
<tr>
<td>General laboratory procedures</td>
<td>Pipettes are regularly calibrated; regular preventive service is performed on instruments; technicians performing assays are trained and certified</td>
</tr>
<tr>
<td>Calibration curve acceptance criteria</td>
<td>For each assay, calibrators must satisfy acceptance criteria to approve a run including: ODblank&lt;0.1; ODblank+calibrator&lt;1.2±3.0; ODblank+calibrator-ODblank+calibrator&lt;0.15±15% for each calibrator</td>
</tr>
<tr>
<td>Internal QC samples</td>
<td>Internal QC samples (aliquots of pooled CSF) are run along patient CSF samples on each plate for run approval; high and low QC samples (in duplicates) are placed both in the beginning and end of the ELISA plate (in total 4 QC samples); the target value has been set by repeated analyses and the SD for acceptability represents the quality standards for the laboratory (often &lt;8%-10%); a run is approved if not more than 1 of the 4 QC samples are outside ±2 SDs of the target value; if any QC samples are outside ±3 SDs, the plate is rerun</td>
</tr>
<tr>
<td>Batch bridging</td>
<td>Two plates of the old and new batches are run in parallel using the same set of individual (n &gt; 20) CSF samples; Bland-Altman²⁵ and Passing-Bablok²⁵ plots are constructed; if there is a systematic difference in absolute concentrations, another batch is evaluated</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; LP, lumbar puncture; OD, optical density; QC, quality control; RT, room temperature; CV, coefficient of variation.

* These procedures are for the ELISA methods for β-amyloid 1-42,²⁶ total tau,²⁷ and phosphorylated tau²⁸ but they can also be applied for other CSF biomarkers after testing for specific characteristics (eg, stability at RT).

18F-flutemetamol PET Scanning, Imaging, Processing, and Analysis

The scanning was performed according to a method described previously²⁹ at 2 sites using the same type of scanner. The analyses of PET images were done at GE Healthcare without knowledge of any diagnostic information (including CSF biomarker levels) of the patients. The processing of the images followed the procedures described by Lundqvist et al.³⁰ The standardized uptake value ratio (SUVR) was defined as the uptake in a volume of interest normalized for the mean uptake in the cerebellar cortex. Positron emission tomographic images were classified as normal or abnormal based on the SUVR of the composite volume of interest. More details about the PET procedures can be found in the Supplement (eAppendix 1).

Measures of Hippocampus Atrophy and Cognition

All patients were examined using a single 3-T magnetic resonance scanner (Triö; Siemens). The images were processed with FreeSurfer version 5.1. The smallest hippocampal volume (left or right) was used in the analyses. Global cognition was rated with the MMSE. Episodic memory was assessed using the Rey Auditory Verbal Learning Test.²¹

Statistical Analysis

The composite SUVR of 18F-flutemetamol was used for all analyses, except for the correlation analyses of the regional SUVR data. An unbiased cutoff value for an abnormal 18F-flutemetamol scan finding was established using mixture modeling.³² The detailed description of the statistical analyses and the software can be found in the Supplement (eAppendix 1). The analyses were performed in the original cohort; the validation cohort was only used to test the CSF Aβ42 threshold established in the original cohort. Either a 95% CI or P < .05 was used to indicate statistical significance.

Results

The characteristics of the original and validation cohorts are shown in Table 2.

CSF Quality Control

Samples of CSF were analyzed in routine clinical practice on different occasions (sample by sample) from September 2011 to September 2013. Longitudinal stability in the measurements during the study was ascertained using an elaborate system of internal quality-control samples and achieved through standardization of the protocols, testing of incoming kit lots, and selection of those that bridged well with previous lots (Table 1). Two internal control samples (aliquots of

Table 2. Characteristics of the Original and Validation Cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original Cohort (n = 118)</th>
<th>Validation Cohort (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective cognitive decline, %</td>
<td>53 (21)</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Amnestic MCI, %</td>
<td>36 (42)</td>
<td>39 (43)</td>
</tr>
<tr>
<td>Nonamnestic MCI, %</td>
<td>11 (15)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.1 (5.4)</td>
<td>69.8 (5.6)</td>
</tr>
<tr>
<td>Female, %</td>
<td>42 (71)</td>
<td>53 (71)</td>
</tr>
<tr>
<td>MMSE score, points</td>
<td>27.8 (1.6)</td>
<td>27.7 (1.9)</td>
</tr>
<tr>
<td>RAVLT score, points</td>
<td>33.5 (10.7)</td>
<td>33.9 (12.2)</td>
</tr>
<tr>
<td>Hippocampus volume, mLb</td>
<td>3.26 (0.50)</td>
<td>3.30 (0.50)</td>
</tr>
<tr>
<td>APOE ε4, 1 or 2 alleles, %</td>
<td>44 (37)</td>
<td>54 (37)</td>
</tr>
<tr>
<td>CSF tau, pg/mL</td>
<td>455 (295)</td>
<td>392 (212)</td>
</tr>
<tr>
<td>CSF Aβ42, pg/mL</td>
<td>701 (307)</td>
<td>806 (116)</td>
</tr>
<tr>
<td>CSF P-tau, pg/mL</td>
<td>61 (32)</td>
<td>52 (20)</td>
</tr>
<tr>
<td>Composite SUVR of 18F-flutemetamol</td>
<td>1.61 (0.50)</td>
<td>1.52 (0.48)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ42, β-amyloid 42; APOE, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; P-tau, phosphorylated tau; RAVLT, Rey Auditory Verbal Learning Test (raw score from the 5 repeated trials); SUVR, standardized uptake value ratio.

* There were no significant differences between the 2 cohorts in any variable.

* The smallest hippocampal volume (left or right side) was chosen.
pooled AD-like and control-like CSF, not the study populations) were analyzed on each enzyme-linked immunosorbent assay plate for quality-control purposes. The coefficients of variation for the quality-control samples ranged from 7.1% to 11.5% for tau, P-tau, and Aβ42 (more details are presented in eAppendix 2 in the Supplement). No correlation was found between any of the CSF biomarkers and the time between the start of the study and the analyses of each CSF sample (r = −0.15 to 0.13, P > .10). This verified that there was no drift in the CSF results over time.

**18**F-flutemetamol PET

The composite SUVR distribution of cortical 18F-flutemetamol retention in the original cohort is illustrated in Figure 1. It indicated 2 overlapping normal distributions suitable for mixture modeling because these constitute 2 different populations—1 with a normal (negative) amyloid deposition and 1 with an abnormal (positive) amyloid deposition. The unbiased cutoff to separate these 2 populations and identify an abnormal cortical Aβ deposition was a composite SUVR of greater than 1.42 (Figure 1; dotted vertical line). With this cutoff, 59 patients (50%) were characterized with abnormal (increased) and 59 (50%) with normal cortical amyloid levels.

**Association Between CSF Biomarkers and 18**F-flutemetamol PET

Next, we studied the association between 18F-flutemetamol PET and CSF biomarkers. Receiver operating characteristic analysis revealed an area under the receiver operating characteristic curve of 0.94 (95% CI, 0.88-0.97) in the original cohort (Figure 2A). The optimal cutoff for CSF Aβ42 to distinguish individuals with an abnormal amyloid PET scan finding from individuals with a normal PET scan finding was 647 pg/mL or less. The cutoff yielded a sensitivity of 95% and a specificity of 90%. This accuracy was equally good among the patients with objective MCI as those with subjective symptoms (eAppendix 2 in the Supplement). The classification accuracy of CSF tau and P-tau to predict an abnormal amyloid PET finding was lower (eFigures 1 and 2A and B in the Supplement). The classification accuracy of CSF Aβ42 to predict cortical amyloid deposition status did not increase if a ratio of Aβ42:tau or Aβ42:P-tau was used (eFigures 1 and 2C and D in the Supplement).

When comparing CSF Aβ42 (dichotomized at ≤647 pg/mL) and 18F-flutemetamol PET (dichotomized at SUVR>1.42) in the original cohort, 92.4% of the patients were categorized identically (tan and blue quadrants in Figure 2B). The corresponding κ value was 0.85 (>0.8 indicates excellent agreement) (Table 3).

The odds ratio for CSF Aβ42 (dichotomized at ≤647 pg/mL) to predict the cortical amyloid PET deposition was 165 (95% CI, 39-693) in the univariate logistic regression analysis with PET SUVR greater than 1.42 as the dependent variable. The predictive value of CSF Aβ42 levels was similar when adjusting for age, sex, education, global cognition (MMSE score), memory function (Rey Auditory Verbal Learning Test), hippocampus volume, and APOE (apolipoprotein E) genotype (odds ratio, 169; 95% CI, 25-1143). This showed that the high agreement between the dichotomized values of CSF Aβ42 and 18F-flutemetamol PET is highly independent of the other variables.

**Regional Aβ PET Deposition and Its Correlations With CSF Analysis**

The cortical 18F-flutemetamol retention in the different brain regions in the original cohort is shown in Table 3. Cerebrospinal fluid Aβ42 levels correlated significantly with the SUVRs of all investigated regions (r = −0.48 to −0.73) (Table 3). The correlation coefficients between CSF Aβ42 and the 18F-flutemetamol SUVRs were higher in cortical regions with high SUVRs (eg, the anterior cingulate and the posterior cingulate and precuneus) and lower in regions with low SUVRs (eg, the medial temporal lobe) (Table 2). Cerebrospinal fluid tau and P-tau followed a more uneven correlation pattern (Table 2).

**CSF Aβ42 and 18**F-flutemetamol PET Characteristics

Among the patients in the original cohort with an increased Aβ deposition (18F-flutemetamol SUVR>1.42), there was no correlation between the values of PET SUVRs and CSF Aβ42 levels (Figure 2B; r = −0.10; P = .45). In this group with an increased amyloid load, 18F-flutemetamol uptake correlated with an impaired global cognitive status (MMSE score; r = −0.32; P = .02), memory function (Rey Auditory Verbal Learning Test; r = −0.28; P = .04), and hippocampus atrophy (r = −0.36; P < .01); however, CSF Aβ42 levels did not correlate with any of these measures.

**Validation Cohort**

We then studied the association between 18F-flutemetamol PET and CSF biomarkers using the cutoffs for CSF Aβ42 and 18F-flutemetamol PET established in the original cohort. In the validation cohort, receiver operating characteristic analysis revealed an area under the curve of 0.91 (95% CI, 0.77-0.98).
When using the previously established optimal cut-off for CSF Aβ42 (≤647 pg/mL), we found that CSF Aβ42 could distinguish patients with normal amyloid PET scan findings from those with abnormal PET scan findings, with a sensitivity of 93% and a specificity of 96% (Figure 2C). In the validation cohort, all but 2 patients (94.7%) were categorized identically according to CSF Aβ42 and the SUVR values of 18F-flutemetamol. C, The AUC was 0.91 in the validation cohort for CSF Aβ42 to predict an abnormal 18F-flutemetamol scan (SUVR > 1.42, as established in the original cohort). The optimal CSF Aβ42 cutoff established in the original cohort was used (=647 pg/mL) to calculate the sensitivity and specificity in this validation cohort (blue dot). D, Scatterplot of the CSF Aβ42 values and the SUVR values of 18F-flutemetamol in the validation cohort. The vertical and horizontal lines represent the CSF and positron emission tomography (PET) cutoffs established in the original cohort. The blue quadrants indicate abnormal PET and CSF; tan quadrants, normal PET and CSF; and light blue quadrants, discordant results (B and D).

Discussion

In this study of nondemented patients with mild cognitive symptoms who were clinically assessed at 3 different clinical sites, we found that levels of CSF Aβ42 were in high agreement with 18F-flutemetamol PET findings and the agreement was independent of APOE genotype, sex, age, education, memory function, global cognition, hippocampus atrophy, and whether the patient had any objective cognitive impairment. The level of CSF Aβ42 identified an abnormal amyloid PET scan, with sensitivities and specificities of more than 90%. Having a CSF Aβ42 level of 647 pg/mL or less meant a more than 100-fold increased probability of having an abnormal amyloid PET scan finding. The main results were replicated in an independent cohort with equally high accuracy.

To our knowledge, it has not previously been studied whether levels of CSF Aβ42 can be used with high validity and reliability to detect abnormal brain Aβ deposition when analyzed consecutively over several years as part of routine clinical practice. Such proof-of-concept studies are needed before one can consider including CSF biomarkers as part of the clini-
Our results are important when considering implementing CSF biomarkers in the clinical workup of early AD diagnosis worldwide. Therefore, in the present study, we analyzed CSF samples on different occasions over 2 years as part of the routine clinical chemistry assessment in an accredited laboratory using multiple different batches of enzyme-linked immunosorbent assay kits, which rendered a variability (coefficients of variation) of 10.2% to 11.5% (CSF Aβ42). The accuracy of CSF Aβ42 measurements in clinical practice for predicting cortical amyloid deposition was surprisingly good given the known issues of variability of CSF biomarker levels due to assay-related preanalytical and analytical factors.34-36 Within- and between-laboratory variability is a general problem for all novel fluid (CSF, plasma, serum, and urine) biomarkers in clinical medicine. A number of standardization initiatives have been initiated to minimize this type of variability for the AD CSF biomarkers including standardized operating procedure for lumbar puncture and sample handling.3 This also includes efforts to develop standardized operating procedures for analytical procedures and assay validation and to develop certified reference materials and methods to serve as gold standards for CSF biomarker measurements.37,38 A suggestion of quality-control procedures at a clinical neurochemistry laboratory is given in Table 1.

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>SUVR of 18F-flutemetamol, Mean (SD)</th>
<th>Correlation With CSF Aβ42</th>
<th>Correlation With CSF Tau</th>
<th>Correlation With CSF P-tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>1.61 (0.50)</td>
<td>−0.69</td>
<td>0.53</td>
<td>0.48</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>1.57 (0.53)</td>
<td>−0.69</td>
<td>0.55</td>
<td>0.50</td>
</tr>
<tr>
<td>Anterior cingulum</td>
<td>1.77 (0.58)</td>
<td>−0.68</td>
<td>0.53</td>
<td>0.48</td>
</tr>
<tr>
<td>Posterior cingulum and precuneus</td>
<td>1.76 (0.55)</td>
<td>−0.72</td>
<td>0.48</td>
<td>0.41</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.52 (0.46)</td>
<td>−0.67</td>
<td>0.49</td>
<td>0.43</td>
</tr>
<tr>
<td>Temporal, lateral</td>
<td>1.66 (0.48)</td>
<td>−0.65</td>
<td>0.56</td>
<td>0.53</td>
</tr>
<tr>
<td>Temporal, medial</td>
<td>1.46 (0.24)</td>
<td>−0.48</td>
<td>0.38</td>
<td>0.39</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.54 (0.36)</td>
<td>−0.57</td>
<td>0.44</td>
<td>0.37</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>1.47 (0.34)</td>
<td>−0.58</td>
<td>0.41</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Table 3. Regional SUVRs of 18F-flutemetamol and Its Correlations With CSF Aβ42, Tau, and P-tau in the Original Cohort

Abbreviations: Aβ42, β-amyloid 42; CSF, cerebrospinal fluid; P-tau, phosphorylated tau; SUVR, standardized uptake value ratios.

a See the Methods section for details.

b The SUVRs were calculated with gray matter in the cerebellum as reference. The SUVR for this region was hence 1 for all patients. The left and right sides have been combined to a mean value. All correlation coefficients were significant (P < .001).

The optimal threshold for defining a pathologic CSF Aβ42 reduction was 647 pg/mL or less, which was cross-validated in an independent cohort. This cutoff was higher than the recommended clinical cutoff at the laboratory (<550 pg/mL) and also according to cutoffs suggested in previous studies.40-43 This indicated that previous measurements could incorrectly have ruled out abnormal amyloid deposition in a subpopulation of patients with incipient AD. It emphasized the importance of using an objective method, such as amyloid PET imaging (and not clinical diagnosis), as the standard of truth when establishing unbiased cutoffs for CSF Aβ42 levels to help avoid problems such as clinical misdiagnoses of dementia cases and the fact that some controls exhibit asymptomatic Aβ accumulation. However, the generalizability of the current cutoff needs to be tested in other laboratories because the between-laboratory variability is relatively high for CSF Aβ42 (about 19%-28%).

The high agreement between CSF Aβ42 levels and 18F-flutemetamol PET in the present study confirmed previous studies comparing CSF Aβ42 measurements (analyzed as part of a research study) and PET imaging (using 18F-florbetapir or 11C-Pittsburgh Compound B).14-16,20-22,44 However, the agreement between CSF Aβ42 measurements and amyloid PET was somewhat higher in the present study when compared with results from the Alzheimer Disease Neuroimaging Initiative (92%-95% agreement in the present study compared with 86% in the Alzheimer Disease Neuroimaging Initiative).29 This difference could be explained by the fact that different methods were used for CSF Aβ42 measurements (INNOTEST vs INNO-BIA AlzBio3) and PET imaging (18F-flutemetamol vs 18F-florbetapir) and different patient populations were examined. Furthermore, we found
in the present study that amyloid PET showed moderate correlations with tau and P-tau (Table 2), which is in accordance with previous studies.4,10,11,18

Among patients with an abnormal amyloid deposition, we found that 18F-flutemetamol PET, but not CSF Aβ42, was associated with hippocampal atrophy and worse global cognition and memory function. Furthermore, 18F-flutemetamol uptake did not correlate with CSF Aβ42 levels among these patients (Figure 2B). This suggested that amyloid PET may be somewhat better than CSF for grading the disease stages of early AD. These data fit with the findings that amyloid PET retention gradually increases slightly over the years in symptomatic AD,39 but CSF Aβ42 levels have already plateaued before the prodromal stages of AD.46,47

In the regional PET analyses, CSF Aβ42 levels correlated best with amyloid PET findings in the regions that had high SUVRs (Table 2), indicating that CSF Aβ42 may reflect the total aggregation status of Aβ42 in the whole brain. The SUVR of 18F-flutemetamol was low in the traditionally most significant AD region, the medial temporal lobe, similar to previous studies,12,19,48 and the correlation with CSF Aβ42 was also low in this region. Using postmortem AD brains, Ni et al49 found that the affinity of Pittsburgh Compound B was higher in the frontal cortex (where total Aβ levels were higher) and lower in the hippocampus (where total Aβ levels were lower), which might explain this result. In contrast, a high regional uptake of 18F-flutemetamol did not necessarily equal a good correlation with CSF tau or P-tau, as in the case of CSF Aβ42 (Table 2). One possible explanation is that the Aβ detected with 18F-flutemetamol PET is not directly correlated with neuronal degeneration or the hyperphosphorylation of tau. However, the presence of (abnormal) Aβ appears important for these 2 processes because there still is a general significant moderate correlation between them (Table 3).

Conclusions

The present results showed that CSF Aβ42 levels can be used to independently predict cortical amyloid deposition during predementia stages with very high accuracy in routine clinical practice and, therefore, can be valuable for the diagnostic workup of early AD. The optimal cutoff level for CSF Aβ42 was 647 pg/mL or less and this threshold was validated in a second cohort. Furthermore, the present results indicated that abnormal 18F-flutemetamol retention levels correlate with disease stage in patients with mild cognitive symptoms; however, this was not the case for CSF Aβ42 measurements.

REFERENCES


