Amyloid-Associated Depression

A Prodromal Depression of Alzheimer Disease?

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Context: A high ratio of plasma amyloid-β peptide 40 (Aβ40) to Aβ42, determined by both high Aβ40 and low Aβ42 levels, increases the risk of Alzheimer disease. In a previous study, we reported that depression is also associated with low plasma Aβ42 levels in the elderly population.

Objective: To characterize plasma Aβ40:Aβ42 ratio and cognitive function in elderly individuals with and without depression.

Design: Cross-sectional study.

Setting: Homecare agencies.

Participants: A total of 995 homebound elderly individuals of whom 348 were defined as depressed by a Center for Epidemiological Studies Depression score of 16 or greater.

Main Outcome Measures: Cognitive domains of memory, language, executive, and visuospatial functions according to levels of plasma Aβ40 and Aβ42 peptides.

Results: Subjects with depression had lower plasma Aβ42 levels (median, 14.1 vs 19.2 pg/mL; P = .006) and a higher plasma Aβ40:Aβ42 ratio (median, 8.9 vs 6.4, P < .001) than did those without depression in the absence of cardiovascular disease and antidepressant use. The interaction between depression and plasma Aβ40:Aβ42 ratio was associated with lower memory score (β = −1.9, SE = 0.7, P = .006) after adjusting for potentially confounders. Relative to those without depression, “amyloid-associated depression,” defined by presence of depression and a high plasma Aβ40:Aβ42 ratio, was associated with greater impairment in memory, visuospatial ability, and executive function; in contrast, nonamyloid depression was not associated with memory impairment but with other cognitive disabilities.

Conclusion: Amyloid-associated depression may define a subtype of depression representing a prodromal manifestation of Alzheimer disease.

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toms of depression may represent a prodromal depression of AD and may lead to a more imminent cognitive deterioration than in those who have a high plasma $\alpha_{40}/\alpha_{42}$ ratio without depression. If our assumption is correct, at the cross-sectional level, patients with amyloid-associated depression should present with a pattern of cognitive impairment consistent with prodromal AD, ie, prominent memory dysfunction, compared with those with nonamyloid depression or those without depression. To test this hypothesis, we investigated the relationships among plasma $\beta$ peptide levels, depression, and cognitive function in a homebound elderly population.

**METHODS**

**STUDY POPULATION AND RECRUITMENT**

We studied a group of 995 subjects, all of whom had been tested for depression status and plasma $\beta$ peptide levels in the Nutrition, Aging, and Memory in the Elderly study, an ongoing, population-based study supported by the National Institute on Aging. Subjects included homebound elderly clients who were enrolled in 1 of 4 home care agencies in the Boston area between 2003 and 2006. Anyone receiving home care services was registered with 1 of these agencies if he or she lived in the city of Boston, had an annual income less than $18,890, and needed home care service. All of the homebound elderly subjects 60 years or older from each of the 4 agencies were invited to participate in the study.

Eligibility for enrollment required that the participants speak English, be physically able to participate in the study home visits, and have sufficient vision and hearing to read and hear the content of the neuropsychological tests. Of all 1803 eligible subjects, 1190 individuals (66.0%) enrolled and gave informed consent to participate in the study. The population was screened with MMSE scores of 10 or less or verbal IQ less than 75 were subsequently examined. Each subject engaged in 3 home visits conducted by a research assistant, who drew a fasting blood sample before the study. After the blood samples were centrifuged immediately after the blood was drawn, the sandwich $\beta$ enzyme-linked immunosorbent assay was used. Plates were coated with 2G3 (anti-$\alpha_{40}$) and 21F12 (anti-$\alpha_{42}$) antibodies overnight at 4°C. Samples were then loaded and incubated overnight at 4°C followed by incubation with a biotinylated monoclonal anti–N-terminus $\beta$ antibody (3D6B) for 2 hours. Finally, streptavidin-conjugated alkaline phosphatase fluorescent substrate (Promega Corp), which was then measured. The lowest detection for both $\beta$ peptides was 1.6 pg/mL. The intracorrelations between 2 different laboratories that have published the results of their $\beta$ measurements showed $r=0.63$ and 0.84 for $\beta_{40}$ and $r=0.90$ and 0.96 for $\beta_{42}$.

**DEFINITION OF DEPRESSION**

Depressive symptoms were assessed by means of the Center for Epidemiological Studies Depression Scale (CES-D)$^{18}$, a CES-D score of 16 or greater was used as the cutoff point for clinical depression.$^{19}$ In 106 subjects in our study, this CES-D cutoff point had a sensitivity of 0.90 and a specificity of 0.83 for the DSM-IV diagnosis of major depression by a board-certified psychiatrist.

Subjects with a CES-D score of 16 or greater and a plasma $\alpha_{40}/\alpha_{42}$ ratio greater than the median (7.1) were defined as having amyloid-associated depression ($n=177$). Those with a CES-D score of 16 or greater and a plasma $\alpha_{40}/\alpha_{42}$ ratio less than or equal to the median were defined as having nonamyloid depression ($n=171$). The other subgroup included those without depression (CES-D score $<16$; $n=647$).

**MEASUREMENTS**

**Cognition**

Research assistants, trained by a board-certified neuropsychologist, administered the following cognitive tests.

1. Digit Symbol: Nine different shapes were coded with the numbers 1 to 9. The subject was given 2 minutes to draw the appropriate shapes in the allotted space according to the code. The total number of correct shapes was recorded. This test was used to evaluate nonverbal general cognition.

2. Wechsler Adult Intelligence Scale III Block Design: The subject was asked to replicate pictures of colored designs by using a set of blocks. Total raw score based on the number of correct designs completed in the given amount of time was recorded to assess both visuospatial and executive functions.

3. Trails B: The subject was asked to perform alternations between numbers and letters while the time of the task was recorded. The cap time was 301 seconds. This test was used to measure executive function.

4. Verbal Fluency (Controlled Oral Word Association Test): The subject was given 1 minute to say as many words as possible that began with a certain letter, 3 separate times. The total number of correct responses to the 3 different letters was recorded. This test was used to measure language ability that is also related to executive function.

5. Wechsler Memory Scale III Logical Memory (LM): Two stories (A and B) were read aloud to the subject; the subject was then asked to repeat as many details from both stories, which were recorded as Delayed Recall. These tests measured a different aspect of memory from word list learning, which is described in the next paragraph.

6. Wechsler Memory Scale III Word List Learning: The subject was read a list of 12 words, 4 separate times. The subject was asked to recall the list after each time it was read. The recall total score was calculated for immediate recall. After 30 minutes, the subject was asked to recall the same list of words against, which was recorded as the Delayed Recall score. These tests were used to measure verbal learning and memory.

**Other Measurements**

Subjects were classified as having CVD according to whether they had been previously informed by a physician that they had con-
gestive heart failure, coronary heart disease, angina pectoris, or a heart attack. Diabetes mellitus was defined as the use of antidiabetic medication or fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) (available on 96% of the samples). Stroke history was recorded. Current hypertension was defined as the average of systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at 2 determinations or was considered present if the subject was taking antihypertensive medications.

A 244–base pair segment of the APOE gene (OMIM 107741), which included the 2 polymorphic sites, was amplified by polymerase chain reaction with a robotic thermal cycler (ABI 877; Applied Biosystems, Foster City, California). The polymerase chain reaction products were digested with 5 U of HhaI, and the fragments were separated by electrophoresis on 8% polyacrylamide nondenaturing gel. The specific allelic fragments were E2, E3, and E4. APOE4 was defined by E4/4, E3/4, or E2/4.21 Renal function, which is associated with plasma Aβ,26 was assessed through measurements of serum creatinine.

STATISTICAL ANALYSIS

Statistical analysis was performed with SAS (version 9.1; SAS Institute Inc, Cary, North Carolina). Mean with standard deviation and t test or analysis of variance were used for the variables with a normal distribution, and median (quartile 1–quartile 3 [Q1-Q3]) and Wilcoxon rank sum test or Kruskal-Wallis test were used for the variables with a skewed distribution. The χ² test was used to compare proportions for binary end points. Subjects’ data were also divided into plasma Aβ quartiles and stratified by depression. Linear regression was used to examine associations between different cognitive domains as an outcome and the interaction between depression and plasma Aβ peptide ratio. The interaction term was added to the model. The correlation between logAβ42 and the different cognitive scores were analyzed by Spearman correlation in each quartile of plasma Aβ42 stratified by depression status. Because Bonferroni correction was applied for regression analyses, the 2-sided significance level of P<.0167 was used.

RESULTS

STUDY POPULATION

Nine hundred ninety-five subjects with depression status and plasma Aβ measurements from the Nutrition, Aging, and Memory in the Elderly study were included in this analysis. The average age of this sample was 75.3 (SD, 8.4) years, and 757 subjects (76.1%) were female. The sample was multiethnic, with 607 (61.0%) white, 375 (37.7%) African American, and 13 (1.3%) other ethnicities. Of 989 subjects who provided information on education, 641 (64.8%) had completed high school.

DEPRESSION AND PLASMA Aβ PEPTIDES

Depression, defined as a CES-D score of 16 or greater, was observed in 346 of the subjects (35.0%). Subjects with depression were younger (mean [SD] age, 73.8 [8.5] vs 76.0 [8.3]; P <.001) and tended to have less education than those without depression, whereas there were no differences in sex and ethnicities between the groups (Table 1). Medically, the depression subgroup had similar APOE4 frequencies, lipid profile, and rates of hypertension, stroke, and diabetes mellitus. Those with depression had higher rates of CVD (51.5% vs 38.6%; P <.001) and were more likely to be taking antidepressants (40.1% vs 21.8%; P <.001) than were those without depression. In addition, subjects with depression tended to have a slightly higher level of creatinine than did those without depression.

Distributions of plasma Aβ peptides were skewed, showing the following levels: Aβ40, median, 132.7 pg/mL; minimum, 1.6 pg/mL; maximum, 1324.9 pg/mL; Aβ42, median, 18.7 pg/mL; minimum, 1.6 pg/mL; maximum, 780.8 pg/mL; and Aβ40: Aβ42 ratio: median, 7.1; minimum, 0.04; maximum, 86.0. Subjects with depression had a lower concentration of plasma Aβ42 (median, 17.1 vs 19.4 pg/mL; P = .02) than did those without depression, but there were no differences in plasma Aβ40 level and Aβ40: Aβ42 ratio between those with and without depression (Table 1). When the subjects with CVD and antidepressant use were removed, those with depression had significantly higher plasma Aβ40: Aβ42 ratios (median, 8.9 vs 6.4; P <.001), lower concentrations of plasma Aβ42 (median, 14.1 vs 19.2 pg/mL; P = .006), and a tendency toward higher concentrations of plasma Aβ40 (median, 138.7 vs 125.9 pg/mL; P = .06) than did those without depression. This result was consistent with our previously published study.19

ASSOCIATION OF COMBINATION OF HIGH PLASMA Aβ40:Aβ42 RATIO AND DEPRESSION WITH COGNITIVE IMPAIRMENT

In this study sample, subjects with depression showed significantly lower scores in every cognitive domain than did those without depression (data not shown). With multivariate linear regression analysis after adjusting for potential confounders including age, education, the APOE4 allele, and medical conditions, the interaction between depression and a high plasma Aβ40: Aβ42 ratio was found to be associated with cognitive impairment (Table 2), especially with memory (LM Delayed Recall: β = -1.9, SE = 0.7, P = .006) and tended to be associated with language (Verbal Fluency: β = -1.8, SE = 0.9, P = .05) and executive function ( Trails B: β = 9.0, SE = 5.7, P = .12). Because plasma Aβ is associated with the preclinical stage of AD,1,2 but the association disappears once the disease occurs,5 we expected that these relationships should be different between those with and without significant cognitive impairment if these associations truly represent a prodromal stage of AD. As shown in Table 2, the interaction between depression and plasma Aβ40: Aβ42 ratio remained associated with cognitive impairment among those with an MMSE score greater than 23 or with an LM Delayed Recall score greater than 14.6 (the norm –1.5 SDs), cutoffs used to exclude cases with severe cognitive impairment including potential cases with dementia in the study sample,23 however, the relationships disappeared among those with...
Regression models were applied to subgroups according to cognitive scores after adjusting for age, school, and logA40:A42 ratio, median (Q1-Q3)

Among those without CVD who used antidepressants

Among those without CVD who did not use antidepressants

Overall

Table 1. Demographic, Medical, and Plasma Aβ Data Among Subgroups With and Without Depression

Table 2. Linear Multivariate-Adjusted Correlates of Each Cognitive Domain as an Outcome

Abbreviations: Aβ, amyloid-β; Aβ42, amyloid-β peptide 42; CVD, cardiovascular disease; HDL, high-density lipoprotein; Q, quartile.

SI conversion factors: To convert total cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4.

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of plasma $\beta_40: \beta_42$ quartile, with a $P$ value of .03 (Figure, A), and this relationship became more significant (mean [SE]: Q1, 18.6 [1.4]; Q2, 18.6 [1.3]; Q3, 14.3 [1.4]; Q4, 13.7 [1.0]; $P = .007$) when the subjects who were using antidepressants were removed (Figure, B). Word Learning List Delayed Recall, which assessed not only memory but also verbal learning, and the other cognitive scores tended to decrease with the increase in each $\beta_40: \beta_42$ quartile but did not reach statistical significance among subjects with depression (Figure, C-E). In contrast, at the cross-sectional level, mean cognitive scores were similar across all quartiles of $\beta_40: \beta_42$ in those without depression (Figure).

ASSOCIATION OF DECREASED PLASMA $\beta_40$ IN DEPRESSION WITH COGNITIVE IMPAIRMENT ONLY AMONG THOSE WITH THE HIGHEST CONCENTRATION OF PLASMA $\beta_40$

To investigate the interplaying role of both peptides, the relationship between plasma $\beta_40$ and cognition was further analyzed within each $\beta_40$ quartile. Among the depressed subjects in the highest plasma $\beta_40$ quartile (Table 3), plasma $\beta_40$ concentration was positively correlated with LM Delayed Recall scores ($r = 0.29, P = .005$) and tended to correlate with MMSE scores ($r = 0.22, P = .04$) and inversely with Trails B scores ($r = -0.23, P = .03$), but was not correlated with verbal fluency. In contrast, all of these correlations between plasma $\beta_40$ and cognitive functions were not observed among nondepressed subjects, even though they also had the highest quartile of plasma $\beta_40$ (Table 3). There was no correlation between plasma $\beta_42$ levels and cognitive function among those in the lower quartiles of plasma $\beta_40$ regardless of depression status (data not shown).

COGNITIVE CHARACTERIZATION OF AMYLOID-ASSOCIATED DEPRESSION

While subjects in the fourth quartile had an $\beta_40: \beta_42$ ratio with a median equal to 14.2, which is near the levels (> 12 to 16) shown to increase the risk of AD in the 2 cohorts, both the fourth and third quartiles showed significantly lower LM Delayed Recall scores than the first or second quartile of $\beta_40: \beta_42$ among subjects with depression (Figure). We therefore used the $\beta_40: \beta_42$ median of the whole sample to define amyloid-associated depression as the following: (1) no depression: CES-D score less than 16; (2) amyloid-associated depression: CES-D score of 16 or greater and $\beta_40: \beta_42$ greater than the median; and (3) nonamyloid depression: CES-D score of 16 or greater and $\beta_40: \beta_42$ ratio less than or equal to the median.

While no differences were found in any of the other variables between the 2 depression subgroups, subjects with amyloid-associated depression were older (mean [SD] age, 74.9 [8.5] vs 72.7 [8.3] years; $P = .01$), had a
Table 4. Comparison of Cognitive Domains Between Subjects With Amyloid-Associated Depression and Those With Nonamyloid Depression

<table>
<thead>
<tr>
<th></th>
<th>Amyloid-Associated Depression (n=735)</th>
<th>Nonamyloid Depression (n=171)</th>
<th>df</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.9 (8.5)</td>
<td>72.7 (8.3)</td>
<td>346</td>
<td>−2.46</td>
<td>.01</td>
</tr>
<tr>
<td>Antidepressant use, No./total (%)</td>
<td>56/173 (32.4)</td>
<td>78/169 (46.2)</td>
<td>1</td>
<td>6.82</td>
<td>.009</td>
</tr>
<tr>
<td>CES-D score, mean (SD)</td>
<td>24.4 (7.3)</td>
<td>24.9 (8.3)</td>
<td>346</td>
<td>0.63</td>
<td>.67</td>
</tr>
<tr>
<td>APOE4, No./total (%)</td>
<td>39/175 (22.3)</td>
<td>34/171 (19.9)</td>
<td>1</td>
<td>0.30</td>
<td>.58</td>
</tr>
<tr>
<td>General cognition</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MMSE score, mean (SD)</td>
<td>24.2 (3.9)</td>
<td>24.9 (3.4)</td>
<td>346</td>
<td>1.82</td>
<td>.15</td>
</tr>
<tr>
<td>Digit Symbol, mean (SD)</td>
<td>31.0 (13.6)</td>
<td>32.6 (14.1)</td>
<td>334</td>
<td>1.04</td>
<td>.32</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design, mean (SD)</td>
<td>18.6 (8.6)</td>
<td>18.8 (8.8)</td>
<td>324</td>
<td>0.65</td>
<td>.59</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B, mean (SD)</td>
<td>236.0 (77.8)</td>
<td>214.1 (84.3)</td>
<td>334</td>
<td>−2.48</td>
<td>.01</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency, mean (SD)</td>
<td>23.9 (10.9)</td>
<td>26.5 (11.7)</td>
<td>342</td>
<td>2.15</td>
<td>.03</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LM Delayed Recall, mean (SD)</td>
<td>15.9 (9.6)</td>
<td>18.9 (9.2)</td>
<td>340</td>
<td>−2.46</td>
<td>.01</td>
</tr>
<tr>
<td>WLL Delayed Recall, mean (SD)</td>
<td>3.0 (2.7)</td>
<td>3.6 (2.6)</td>
<td>342</td>
<td>1.94</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; LM, Logical Memory; MMSE, Mini-Mental State Examination; WLL, Word List Learning.

Table 5. Multivariate-Adjusted Correlates of Each Cognitive Domain as an Outcome in Subjects Without Depression Combined With Those With Either Amyloid-Associated Depression or Nonamyloid Depression

<table>
<thead>
<tr>
<th></th>
<th>Subjects With Amyloid-Associated Depression + Without Depression (n=735)</th>
<th>Subjects With Nonamyloid Depression + Without Depression (n=704)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LM Delayed Recall (n=735) Block Design (n=710)</td>
<td>LM Delayed Recall (n=730) Block Design (n=704)</td>
</tr>
<tr>
<td></td>
<td>β Estimate (SE) P Value</td>
<td>β Estimate (SE) P Value</td>
</tr>
<tr>
<td>Age, y</td>
<td>−0.3 (0.04) &lt;.001</td>
<td>−0.2 (0.04) &lt;.001</td>
</tr>
<tr>
<td>School, y</td>
<td>0.9 (0.1) &lt;.001</td>
<td>0.8 (0.1) &lt;.001</td>
</tr>
<tr>
<td>APOE4</td>
<td>−1.5 (0.7) .04</td>
<td>−2.0 (0.7) .005</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>1.3 (0.8) .09</td>
<td>0.1 (0.7) .87</td>
</tr>
<tr>
<td>Amyloid-associated depression</td>
<td>−1.9 (0.4) &lt;.001</td>
<td>−1.4 (0.4) &lt;.001</td>
</tr>
<tr>
<td>Nonamyloid depression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: LM, Logical Memory.

All of the listed variables were included in the regression model after adjusting for sex, race, creatinine level, diabetes mellitus, stroke, and cardiovascular disease. Because Bonferroni correction was applied, P<.0167 is considered significant.

slightly higher level of creatinine (mean [SD], 1.3 [1.2] vs 1.1 [1.0] mg/dL; P=.01) (to convert creatinine to micromoles per liter, multiply by 88.4), and were less likely to take antidepressants (32.4% vs 46.2%; P=.009) than were those with nonamyloid depression (Table 4).

Although there was no difference in CES-D scores between the 2 subgroups, those with amyloid-associated depression had poorer memory scores in the LM Delayed Recall (mean [SD], 15.9 [9.6] vs 18.9 [9.2]; P=.004) and tended to have lower Word Learning List Delayed Recall scores (mean [SD], 3.0 [2.7] vs 3.6 [2.6]; P=.05), lower language ability (Verbal Fluency mean [SD], 23.9 [10.9] vs 26.5 [11.7]; P=.03), and lower executive function (Trails B test mean [SD], 236.0 [77.8] vs 214.1 [84.3]; P=.01) than did those with nonamyloid depression (Table 4). In contrast, scores evaluating general cogni-

...
Recall: symptom of AD. A neuropathology study has shown those with nonamyloid depression (Table 4).

There is growing evidence in the literature that depression is associated with increased amyloid plaques and neurofibrillary tangles, which are the neuropathological hallmarks of AD. The pattern of cognitive impairment, prominently poor memory, in amyloid-associated depression (Table 4 and Figure), and (2) nonamyloid depression, which is associated with only visuospatial and executive dysfunction (Table 5). Because a high plasma Aβ40: Aβ42 ratio increases the risk of AD prospectively, we hypothesize that amyloid-associated depression is more likely to be a prodromal stage of AD than is a high Aβ40: Aβ42 ratio without depression. Antidepressants, specifically selective serotonin reuptake inhibitors, have been shown to be associated with lower concentration of plasma Aβ42 than did those with nonamyloid depression (Table 4).

There is growing evidence in the literature that depression may be either a risk factor for AD 2, 24-27 or an early symptom of AD. A neuropathology study has shown that history of depression is associated with increased amyloid plaques and neurofibrillary tangles, which are the neuropathological hallmarks of AD. The pattern of cognitive impairment, prominently poor memory, in amyloid-associated depression (Table 4 and Figure) is consistent with mild cognitive impairment (MCI), which is presumed to be a prodromal stage of AD. Although MCI is associated with depression, depression is also found to increase the risk of developing MCI.

The severity of depressive symptoms was correlated with lower concentration of plasma Aβ42, a determining factor of Aβ40:Aβ42 ratio, only when CVD cases were excluded from the study sample. Most likely there are different subtypes of depression in the elderly population, including (1) early-onset depression, (2) poststroke depression, (3) vascular depression related to CVD and other vascular risk factors that lead to executive dysfunction, (4) preclinical depression of AD, and (5) comorbid depression in AD. Because these depression subtypes have different underlying pathological characteristics and prognoses, not all should be related to plasma Aβ levels, or they may be related to plasma Aβ levels differently. In contrast to amyloid-associated depression, nonamyloid depression was not found to be associated with memory (Table 5) even though these subjects had higher levels of plasma Aβ42 than did those without depression. Although the rates of CVD (92 of 171 [53.8%] vs 82 of 177 [46.3%]; P = .32) and stroke (31 of 171 [18.1%] vs 35 of 177 [19.8%]; P = .89) were similar between subjects with nonamyloid depression and those with amyloid-associated depression, cerebral microvascular pathological data in these cases is unknown. Regardless, nonamyloid depression was strongly associated with a cognitive pattern of vascular depression and visuospatial and executive dysfunction (Table 5). This and other factors may explain the seemingly conflicting result in another study in which depressed patients had a higher, not lower, level of plasma Aβ42 than the controls.

It is intriguing to find that the combination of 2 peptides in plasma, a high level of Aβ40 and a low level of Aβ42, was associated with poor memory, whereas each peptide alone was not found to have this relationship in the regression analysis (Table 3). The peptides Aβ42, a major component of AD pathological findings in the brain, and Aβ40, a component of cerebral amyloid angiopathy, are produced by the processing of APP. Although plasma Aβs reflect dynamic levels governed by both peripheral11-14 and central15 nervous system origins, these 2 peptides in plasma have been linked to pathological conditions in the brain. First, high plasma Aβ40 level is associated with cerebral microvascular pathological changes, white matter hyperintensities, and lacunar infarcts. Both white matter hyperintensities and lacunar infarcts are linked to cognitive impairment, dementia incidence, and depression in the elderly population. Second, studies using APP transgenic mice have demonstrated that plasma Aβ42 level declines significantly before Aβ42 is deposited in the brain to form the AD changes. Therefore, a high Aβ40:Aβ42 ratio in plasma may be a biomarker to indicate cerebral microvascular pathological changes, which are associated with high plasma Aβ40 level, coexisting with the AD pathological features, which may be linked to plasma Aβ42 decline at the preclinical stage. These 2 pathological conditions in the brain additively or synergistically result in more severe cognitive dysfunction than either condition alone.

Plasma Aβ level correlates with cerebrospinal fluid Aβ concentration in APP transgenic mice when they are young and pathological changes of AD have not yet formed. However, this correlation disappears as the animals age and Aβ is deposited in the brain. Similarly in humans, although plasma Aβ level cannot be used for the diagnosis of AD, it is still possible that plasma Aβ level can be used as a screening tool for the risk of AD. In this study, the relationship between poor memory and a high plasma Aβ40:Aβ42 ratio in depression was observed among subjects with normal cognition or MCI, but the relationship disappeared among those with severe cognitive impairment (Table 2). Two large population studies, mainly containing patients with late-onset
AD, have shown that a high plasma Aβ42/Aβ40 ratio, determined by both low Aβ42 and high Aβ40 levels, increases the risk of AD prospectively.1,12 Although another population study reports that high plasma Aβ42 level is associated with the risk of AD,33 plasma Aβ42 level declines in these subjects before the onset of the disease, leading to low levels of plasma Aβ40 at the prodromal stage. Unlike late-onset AD, both early-onset AD56 and Down syndrome27–29 present with high plasma Aβ42 level at the preclinical stage. Another study shows that patients with MCI have higher levels of plasma Aβ42 than do controls but only in women.60 It is not yet known whether plasma Aβ status is different at the preclinical stage of AD with and without depression. Because only a subset of the patients with late-onset AD present with depression at the start of the disease, our data suggest that the combination of depressive symptoms and plasma Aβ level may more specifically inform the prodromal stage of AD than does either one status alone.

Although our study found that amyloid-associated depression presented with poor memory, and others hypothesized that elevated plasma Aβ42 level in depression may contribute to AD,48 without a longitudinal study we cannot yet conclude that amyloid-associated depression vs non-amyloid depression is a precursor of AD. We have used different analytical methods and applied Bonferroni correction to prevent against type I error, but the cross-sectional design is still the major limitation of our study. Other limitations include the following: (1) depression was based on the CES-D score rather than the DSM-IV criteria, and we had no information about the onset and the course; (2) some variables, such as CVD and stroke, were self-reported; (3) the complexity of plasma Aβ40,42 requires brain investigation to validate amyloid-associated depression as a unique depression subtype; (4) although our assays in measurement of Aβ40 vs Aβ42 in plasma had high sensitivity and specificity, the field lacks standard assays for interlaboratory comparisons; and (5) the correlation coefficients shown in Table 3 were significant, but probably not large enough to be applied in clinical practice. Nevertheless, our discoveries have found the relationship between depression severity and low plasma Aβ42 level and further have linked a high plasma Aβ40/Aβ42 Ratio in depression with poor memory, especially among those with normal or mildly impaired cognition. Our findings warrant prospective studies to examine whether amyloid-associated depression is related to pathalogical changes in the brain and predict the onset of cognitive decline and AD in this and other populations.

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