Metabolism of Amyloid-β Protein May Be Affected in Depression

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ABSTRACT

Objective: Epidemiologic studies have demonstrated that a history of depression increases the risk of developing Alzheimer's disease, particularly among individuals with early-onset depression. On the other hand, recent studies have suggested that a higher amyloid-β protein (Aβ)40 to Aβ42 ratio may be associated with the future onset of Alzheimer's disease. Our objective was to assess whether the pathophysiology of early-onset depression may involve or affect Aβ metabolism.

Method: In this extension of a case-control pilot study, 193 inpatients with *DSM-IV* major depressive disorder (MDD) (mean age = 55.9 years) from the Juntendo Koshigaya Hospital, Saitama, Japan, and 413 healthy controls from the community (mean age = 56.6 years) were recruited between May 2004 and April 2009. Serum Aβ40 and Aβ42 levels, Aβ40/Aβ42 ratio, and other clinical and biological factors were compared between controls and patients in 3 age groups: young (< 40 years), middle-aged (≥ 40 to < 65 years), and elderly (≥ 65 years). Depressive symptoms were assessed with the Hamilton Depression Rating Scale. All patients were receiving antidepressant medication at the time of the study, and doses of current antidepressants were converted to an equivalent imipramine dose.

Results: The serum Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls in all age groups (young: $P = .003$; middle-aged: $P < .001$; elderly: $P = .006$). These differences were also observed in noncarriers of the apolipoprotein E ε4 allele.

Conclusions: Our findings suggest that Aβ metabolism may be affected in depression; these findings also possibly answer the question of why even early-onset depression is a risk factor for developing Alzheimer's disease.

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See also Commentary on page 113.

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Epidemiologic studies have demonstrated that depression may increase the risk for Alzheimer's disease (AD).[1–3] This association has been shown even in individuals in which depression occurred long before the onset of AD.[4] The recent Rotterdam Scan Study[5] supported the idea that a history of depression increases the risk of developing AD, particularly among individuals with early-onset depression.

Neuropathology of the brain in individuals with AD is characterized by the presence of extracellular senile plaques and intracellular neurofibrillary tangles. The major protein component of senile plaques is amyloid-β protein (Aβ), a 40– or 42–amino acid peptide cleaved from the amyloid precursor protein by β-secretase and γ-secretase. Amyloid-β is normally present in the brain, cerebrospinal fluid, and peripheral blood. In cerebrospinal fluid, the concentration of Aβ42 is reduced in patients with AD and in those with the mild cognitive impairment that precedes AD,[6,7] suggesting an association with selective deposition of Aβ42 in the brain. The relationship between cerebrospinal fluid and plasma Aβ levels remains unclear.[8–10] In the transgenic mouse model of AD, plasma Aβ levels have been shown to decline in parallel with cerebrospinal fluid Aβ as Aβ is deposited in the brain.[11] However, contrary to results seen in animal studies, results of plasma Aβ levels in patients with AD have been contradictory.[12–15] Recent large cohort studies[16–18] have also shown that a low plasma Aβ42 level combined with a high Aβ40 level increases the risk of developing AD, and it has been concluded that a higher plasma Aβ40/Aβ42 ratio may be useful for identifying patients at risk for developing mild cognitive impairment and AD.

In terms of depression, elevated plasma Aβ42 levels and a lower Aβ40/Aβ42 ratio have been reported in patients with late-life depression.[19] Conversely, lower plasma Aβ42 levels[20,21] and a higher Aβ40/Aβ42 ratio have been reported in elderly individuals with depression, suggesting that *amyloid-associated depression* may define a subtype of depression representing a prodromal manifestation of AD.[22] We recently reported[23] that the serum Aβ40/Aβ42 ratio was significantly higher in patients with major depressive disorder (MDD) than in controls, and this difference was seen not only for elderly individuals but also for younger individuals (aged < 60 years), suggesting that depression is not merely a prodromal manifestation of AD. Accordingly, several studies[19–22] of Aβ levels in the peripheral blood of elderly individuals with depression have been reported in the literature, but no report supports or explains the above-mentioned epidemiologic findings in terms of any correlation between early-onset depression and onset of AD.

The aim of the present study was to reveal whether the pathophysiology of early-onset depression may involve or affect Aβ metabolism. Thus, we examined serum Aβ40 and Aβ42 levels and the Aβ40/Aβ42 ratio in young (< 40 years), middle-aged (≥ 40 to < 65 years), and elderly (≥ 65 years) MDD patients and healthy controls. In addition, we investigated the relationships between Aβ, apolipoprotein E ε4 allele (ApoE4), various serum markers, and clinical features in MDD patients and controls. This study is a part of the Juntendo University Mood Disorder Project (JUMP).

METHOD

Participants

A total of 211 inpatients with depression were recruited from Juntendo Koshigaya Hospital, Saitama, Japan, between May 2004 and April 2009. All patients met

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DSM-IV criteria for MDD. Patients were excluded if they had a history of other psychiatric disorders including delusions, severe or acute medical illnesses, neurologic disorders, or use of drugs that may cause depression. Patients showing clinical evidence of dementia or with Mini-Mental State Examination (MMSE)[24] scores < 24 were also excluded (n = 18 for all exclusions). Finally, 193 inpatients with MDD (74 men, 119 women; mean age = 55.9 years; age range, 27–83 years) were enrolled in this study. Depressive symptoms were assessed with the Hamilton Depression Rating Scale.[25] Previous depressive episodes defined as depression included depressive episodes that had required the attention of a general practitioner, psychologist, or psychiatrist.[5] All patients were receiving antidepressant medication at the time of the study. The doses of antidepressants were converted to an equivalent dose of imipramine.[26] The number of depressive episodes and total duration of medication use were confirmed via medical records.

A total of 450 healthy participants were recruited as a control group. Controls who had any history of depression, dementia, or other neuropsychiatric disease (n = 18) or MMSE scores < 24 (n = 19) were also excluded. Finally, 413 healthy participants (181 men, 232 women; mean age = 56.6 years; age range, 18–83 years) were enrolled as a control group. All controls were working at least part-time or were students (229 were employees of medical or welfare facilities, 175 were from a temporary employment agency for older people, and 9 were university students).

We divided both MDD patients and controls into 3 age groups (young: < 40 years; middle-aged: ≥ 40 to < 65 years; and elderly: ≥ 65 years). Results were then compared within age groups.

The study protocols of this extension of our case-control pilot study were approved by the Medical Ethics Committee of Juntendo University, Tokyo, Japan, and were performed in accordance with the regulations outlined by Juntendo University. All participants provided written informed consent prior to participation.

Serum Aβ40 and Aβ42 Measurements

Blood samples were drawn into serum separator tubes with the separator gel and were centrifuged immediately (VenoJect II; Terumo Corporation, Tokyo, Japan). Serum samples were stored at −80°C until use. A sandwich Aβ enzyme-linked immunosorbent assay kit was used (Wako Pure Chemical Industries, Osaka, Japan). The Aβ40 kit uses the BAN50 monoclonal antibody, which specifically detects the N-terminal portion of human Aβ (1-16), and the BA27 monoclonal antibody, which detects the C-terminal portion of Aβ (1-40). The Aβ42 kit uses the BAN50 monoclonal antibody, as well as the BC05 monoclonal antibody, which detects the C-terminal portion of Aβ (1-42). The sensitivity was 0.019 pmol/L (dynamic range: 1.0–100.0 pmol/L) for Aβ40 and 0.06 pmol/L (dynamic range: 0.1–20.0 pmol/L) for Aβ42.[23] The *intra-assay* coefficients of variation were 4.8% at a mean of 14.2 pmol/L, 4.3% at a mean of 36.0 pmol/L, and 3.6% at a mean of 75.5 pmol/L (n = 24) for Aβ40 and were 0.8% at a mean of 3.2 pmol/L, 0.8% at a mean of 7.4 pmol/L, and 1.0% at a mean of 16.4 pmol/L (n = 24) for Aβ42. The *interassay* coefficients of variation were 3.2% at a mean of 14.8 pmol/L, 1.1% at a mean of 33.6 pmol/L, and 2.5% at a mean of 75.7 pmol/L (n = 5) for Aβ40 and were 8.3% at a mean of 3.2 pmol/L, 11.3% at a mean of 7.1 pmol/L, and 5.8% at a mean of 16.4 pmol/L (n = 6) for Aβ42.

- Changes in amyloid-β (Aβ) metabolism may be a biological factor in the transition from depression to Alzheimer's disease (AD).
- Clinicians should follow up even with younger patients with major depressive disorder (MDD) and consider them to be at high risk for AD.
- Higher blood Aβ40/Aβ42 ratio in patients with MDD may be an index for future preventive therapy for AD, such as amyloid vaccination.

Clinical Points

Other Biological Measurements

Apolipoprotein E genotypes for all samples were determined according to a previous report.[27] Serum levels of total protein, aspartate aminotransferase, alanine aminotransferase, creatinine, total cholesterol, triglycerides, and glucose were also measured (BML Inc [clinical laboratory test service], Tokyo, Japan).

Data Analysis

For statistical analysis, age, education, MMSE score, and serum levels of total protein, aspartate aminotransferase, alanine aminotransferase, creatinine, total cholesterol, triglycerides, and glucose were compared between the MDD group and controls using the 2-tailed unpaired Student *t* test; the χ^2 test was used to compare the variables of sex and ApoE4. Serum Aβ40 and Aβ42 levels and the Aβ40/Aβ42 ratio were compared using the Mann-Whitney *U* test; median values were used for variables with skewed distribution.[16,22] A significance level of $P < .05$ was used. Bonferroni correction was applied; a 1.67% level of significance was used for the 3 age-group comparisons. The Aβ40 and Aβ42 levels and Aβ40/Aβ42 ratios were transformed to $\log_{10}$ for multiple regression analysis because of the skewed distribution of Aβ variables.[22] Statistical procedures were performed using the Japanese version of SPSS, software version 15.1 (SPSS Japan, Tokyo, Japan).

RESULTS

Detailed demographic and clinical features of participants are shown in Table 1. No significant differences in age, gender, education, MMSE score, ApoE4 frequencies, or serum levels of total protein, aspartate aminotransferase, alanine aminotransferase, creatinine, total cholesterol, triglycerides,

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Table 1. Demographic and Other Variables Among MDD Patients and Controls (N = 606)

Variable	MDD (n = 193)	Controls (n = 413)	*P* Value
Age, mean (SD), y	55.9 (14.7)	56.6 (14.7)	.57[a]
Gender, male/female, n	74/119	181/232	.22[b]
Education, mean (SD), y	13.2 (2.5)	12.6 (3.1)	.20[a]
Total protein, mean (SD), g/dL	7.2 (0.6)	7.3 (0.4)	.14[a]
Aspartate aminotransferase, mean (SD), U/L	21.4 (16.9)	22.5 (9.2)	.38[a]
Alanine aminotransferase, mean (SD), U/L	15.3 (17.0)	14.3 (9.9)	.42[a]
Creatinine, mean (SD), mg/dL	0.7 (0.2)	0.7 (0.2)	.75[a]
Total cholesterol, mean (SD), mg/dL	201.9 (42.8)	205.1 (34.9)	.44[a]
Triglycerides, mean (SD), mg/dL	131.9 (75.7)	132.9 (73.4)	.91[a]
Glucose, mean (SD), mg/dL	109.7 (27.4)	109.6 (27.9)	.97[a]
HDRS score, mean (SD)	20.0 (8.7)	0.8 (2.0)	< .001[a]
No. of depressive episodes, mean (SD)	1.7 (1.1)	NA	
Total duration of medication, mean (SD), mo	31.4 (46.6)	NA	
Total dose of antidepressant, mean (SD), mg/d[d]	130.0 (75.9)	NA	
MMSE score, mean (SD)	27.2 (2.2)	26.9 (2.4)	.15[a]
Apolipoprotein E ε4 carrier, n (%)	38 (19.7)	84 (20.3)	.91[b]
Serum amyloid-β protein (Aβ), median (Q1–Q3)			
Aβ40, pmol/L	25.5 (19.5–35.4)	25.9 (18.0–35.7)	.51[c]
Aβ42, pmol/L	2.2 (1.0–4.1)	2.6 (1.8–4.3)	< .001[c]
Aβ40/Aβ42 ratio	11.8 (7.5–22.5)	8.6 (6.3–12.2)	< .001[c]

[a]Student *t* test. [b]χ^2 test. [c]Mann-Whitney *U* test. [d]Antidepressants were converted into equivalent doses of imipramine.
Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, NA = not applicable, Q = quartile.

or glucose were seen between MDD patients and controls. The Hamilton Depression Rating Scale score was significantly higher in MDD patients than controls ($P < .001$). There were no differences in serum Aβ40 levels between MDD patients and controls; however, serum Aβ42 levels were significantly lower ($P < .001$) and the Aβ40/Aβ42 ratio significantly higher ($P < .001$) in patients with MDD compared with controls (Table 1).

Serum Aβ40 levels were not different between MDD patients and controls in any age group (Table 2). Young ($P = .017$) and middle-aged ($P = .06$) patients with MDD showed trends to have a lower level of serum Aβ42 than controls, and values were significantly lower in the elderly group compared with controls ($P = .009$). The Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls in all age groups (young: $P = .003$; middle-aged: $P < .001$; elderly: $P = .006$). Even if subjects with an MMSE score < 28 (n = 59 in MDD, n = 174 in controls) were excluded, the Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls ($P < .001$).

The ApoE4 frequencies were similar between MDD patients and controls in all age groups. Even in the analysis using noncarriers of the ApoE4 allele, results were almost the same as above (Table 2). Serum Aβ40 levels did not differ significantly between MDD patients and controls in any age group of ApoE4 noncarriers. Serum Aβ42 levels in patients with MDD were significantly lower in the young group ($P = .01$) compared with controls and showed a trend to be lower in the middle-aged ($P = .04$) and elderly ($P = .03$) groups compared with controls. In noncarriers of ApoE4, young ($P = .003$) and middle-aged ($P < .001$) patients with MDD had a significantly higher Aβ40/Aβ42 ratio than controls; these values showed a trend to be higher in the elderly group compared with controls ($P = .06$).

The age of the MDD patients showed a trend to be higher than that of controls in the young group ($P = .03$) and was significantly higher in MDD patients than controls in the elderly group ($P = .01$). Gender was not matched in the middle-aged ($P = .002$) and elderly ($P < .001$) groups. However, multiple regression analysis showed that age, gender, Hamilton Depression Rating Scale score, number of depressive episodes, total duration of medication use, and total dose of antidepressant did not influence the Aβ40/Aβ42 ratio (Table 3).

Table 2. Demographic and Other Data Among MDD Patients and Controls by Age Group (N = 606)

	Young (< 40 y)			Middle-Aged (≥ 40 to < 65 y)			Elderly (≥ 65 y)		
Variable	MDD (n = 34)	Controls (n = 70)	*P* Value[a]	MDD (n = 95)	Controls (n = 183)	*P* Value[a]	MDD (n = 64)	Controls (n = 160)	*P* Value[a]
Age, mean (SD), y	34.0 (3.3)	30.6 (6.2)	.03[b]	53.0 (7.5)	55.2 (7.1)	.15[b]	72.0 (5.5)	69.7 (3.8)	.01[b]
Gender, male/female, n	20/14	31/39	.21[c]	40/55	44/139	.002[c]	14/50	106/54	< .001[c]
ApoE4 carrier, n (%)	6 (17.6)	13 (18.6)	1.00[c]	18 (18.9)	40 (21.9)	.64[c]	14 (21.9)	31 (19.4)	.71[c]
Serum Aβ, median (Q1–Q3)									
Aβ40, pmol/L	23.6 (17.4–28.0)	25.0 (14.8–33.0)	.86[d]	25.7 (20.0–34.7)	23.4 (16.6–31.4)	.13[d]	27.2 (21.6–39.8)	32.2 (22.7–42.4)	.34[d]
Aβ42, pmol/L	2.2 (1.0–4.7)	3.0 (2.1–6.4)	.017[d]	2.4 (0.9–3.8)	2.5 (1.6–3.9)	.06[d]	1.7 (1.0–4.2)	2.8 (1.8–4.8)	.009[d]
Aβ40/Aβ42 ratio	9.6 (4.1–23.3)	6.5 (2.1–8.8)	.003[d]	11.7 (7.4–21.1)	8.6 (6.5–11.7)	< .001[d]	13.0 (9.3–24.7)	9.9 (7.5–13.8)	.006[d]
Serum Aβ among ApoE4 noncarriers, median (Q1–Q3)	(n = 28)	(n = 57)		(n = 77)	(n = 143)		(n = 50)	(n = 129)	
Aβ40, pmol/L	23.6 (17.6–28.1)	25.0 (14.7–33.0)	.82[d]	25.6 (19.4–33.8)	23.1 (15.9–31.0)	.21[d]	27.2 (21.7–41.6)	33.4 (24.9–43.0)	.18[d]
Aβ42, pmol/L	1.3 (0.9–4.6)	3.0 (2.0–6.8)	.01[d]	1.7 (0.9–3.4)	2.4 (1.6–3.6)	.04[d]	2.1 (1.1–4.6)	3.4 (2.0–5.3)	.03[d]
Aβ40/Aβ42 ratio	16.5 (4.0–25.9)	6.4 (2.1–9.2)	.003[d]	12.5 (8.2–21.9)	9.1 (7.0–11.9)	< .001[d]	11.3 (8.5–23.5)	9.0 (7.4–14.1)	.06[d]

[a]Bonferroni correction was applied, and a 1.67% level of significance was adopted. [b]Student *t* test. [c]χ^2 test. [d]Mann-Whitney *U* test.
Abbreviations: Aβ = amyloid-β protein, ApoE4 = apolipoprotein E ε4, MDD = major depressive disorder, Q = quartile.

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Table 3. Results of Multiple Regression Analysis of Aβ40/Aβ42 Ratios

	Log_{10} Aβ40/Aβ42 Ratio[a]	
Variable	β Estimate (SE)	*P* Value
Age, y	−0.006 (0.010)	.57
Sex	−0.189 (0.210)	.37
HDRS score	0.004 (0.010)	.73
No. of depressive episodes	0.073 (0.130)	.59
Total duration of medication, mo	−0.001 (0.003)	.74
Total dose of antidepressant, mg/d[b]	0.001 (0.002)	.49

[a]Aβ40/Aβ42 ratio values were transformed to log_{10} (log Aβ) because of the skewed distributions.
[b]Antidepressant doses were converted into equivalent imipramine doses.
Abbreviations: Aβ = amyloid-β protein, HDRS = Hamilton Depression Rating Scale.

DISCUSSION

In the present study, serum Aβ42 levels were significantly lower in elderly subjects compared with controls and trended toward being lower in young and middle-aged patients. Furthermore, the Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls in all age groups. These findings were also observed in noncarriers of ApoE4. Our most important finding was that the Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls, even in middle-aged and young individuals.

Epidemiologic studies[4,5] have demonstrated that both late-onset and early-onset depression are risk factors for AD. The MIRAGE Study[4] evaluated the association between depression and the risk of AD in 1,953 patients with AD and 2,093 of their unaffected family members. The study demonstrated that depressive symptoms were associated with the development of AD, even in families in which the first symptoms of depression occurred more than 25 years before the onset of AD, suggesting that depression is a risk factor for later development of AD. The Rotterdam Scan Study[5] was a large population-based prospective study in which 503 elderly individuals were followed for an average of 6 years to check for development of AD. Results showed that a history of late-onset depression increased the risk for AD (hazard ratio = 2.34), whereas individuals with a history of early-onset depression showed an even greater risk (hazard ratio = 3.76).[5] These results suggest that even early-onset depression may have some relationship to the pathology of AD. The glucocorticoid cascade hypothesis[28] has been generally accepted as the rationale for why early-onset depression leads to AD, based on the damaging effect of glucocorticoids on the hippocampus. However, the Rotterdam Scan Study[5] could not find a significant association between a history of depression and hippocampal volume. These researchers raised the possibility that another unknown factor leads to an increased risk for AD. Combining these previous reports and our findings, one may speculate that some individuals with MDD have pathological changes in amyloid metabolism (including Aβ production, aggregation, deposition, and/or excretion). Interestingly, patients with AD with a history of depression have been shown to have higher levels of amyloid plaque in the brain than those without a history of depression.[29]

In late-life depression, especially in late-onset depression, vascular changes in subcortical gray matter and white matter are more prevalent and severe than in age-matched controls.[30–35] Cerebral vascular changes in patients with late-life MDD are associated with executive dysfunction even in a remitted state, suggesting that cerebral vascular changes may affect continuous cognitive dysfunction in elderly patients with MDD.[36] These previous reports suggest that depression may be a preclinical symptom of dementia, including AD, for some patients with late-life MDD who have cerebral vascular disease. However, these findings do not explain why early-onset depression may be a risk factor for developing AD.

Peripheral Aβ levels have been examined only in elderly depression.[19–22,37–39] Pomara and Murali Doraiswamy[39] first raised the possibility of Aβ abnormalities in depression, and they reported higher plasma Aβ42 levels in elderly depression.[19] In contrast, Qiu et al[20] and Sun et al[21,22,37] reported lower plasma Aβ42 levels and a higher Aβ40/Aβ42 ratio in a large sample of elderly depressive individuals. Sun et al[22] suggested that exclusion of depression with cardiovascular disease in their study is the main reason for the discrepancy between the 2 studies and that depressive individuals with a higher Aβ40/Aβ42 ratio may have preclinical or early-stage AD.

The ApoE4 allele leads to accelerated deposition of amyloid and is a major genetic risk factor for AD.[40] The frequency of the ApoE4 allele in patients with MDD may explain the relation between depression and AD. However, previous reports[41,42] and the present study showed no association between ApoE4 carriers and depression. Irie et al[43] also reported that depressed individuals without ApoE4 had a 1.6-fold greater risk for dementia.

In the present study, all patients with MDD were receiving antidepressant medication, and it is possible that serum Aβ levels might have been influenced by this medication. However, multiple regression analysis showed that total duration of medication use and total dose of antidepressant were not associated with Aβ40/Aβ42 ratio. Pomara et al[19] found no significant effect of antidepressant treatment on plasma Aβ42 levels, consistent with our results. Sun et al[21] also found no difference in plasma Aβ42 levels between depressed individuals who did and did not receive treatment with antidepressants. Meanwhile, patients receiving antidepressants showed lower plasma Aβ40 levels than those not receiving antidepressants.[21] A study[44] using a transgenic mouse model of AD showed that levels of Aβ and number of Aβ-immunoreactive neurons were significantly reduced in the hippocampus of paroxetine-treated mice. Accordingly, antidepressant therapy is unlikely to be a major factor that influences the higher Aβ40/Aβ42 ratio shown in patients with MDD in this study. It has been reported that lithium[45,46] and valproic acid[47] influence Aβ secretion. In the present study, 18 patients were taking lithium and 17 patients were

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taking valproic acid. When we excluded these patients, the fundamental results did not change (data not shown), suggesting that treatment with lithium or valproic acid did not influence our results.

There are various serum factors in the peripheral blood that may influence Aβ metabolism. Previous studies concerning Aβ levels in peripheral blood have not examined these serum factors. This article is the first to report correlations between Aβ levels and other serum factors; none of these factors appeared to affect Aβ levels in this study.

The present study is an extension of our pilot study.[23] Although higher Aβ40/Aβ42 ratios in older and younger patients with MDD were found in both studies, the pilot study showed higher Aβ40 levels and no differences in Aβ42 levels in younger patients with MDD, which is inconsistent with the present study. In the pilot study, raw data obtained from only 30 individuals in each group were simply compared even though they showed a relatively wide variation. Therefore, we analyzed the data again and found that 3 young MDD patients, 1 elderly MDD patient, and 2 elderly controls had a deviated value (higher Aβ40 and/or Aβ42 than the mean + 2 SDs in each group). No consistent factors were found among the individuals in terms of biochemical data examined, and it cannot be explained why they showed such deviated values. However, if the data from these 6 individuals were excluded, Aβ40 levels showed no significant differences between MDD patients and controls, and Aβ42 levels were significantly lower ($P = .014$) in young MDD patients compared with controls. Moreover, results in the elderly group did not differ from those before these 6 patients were excluded. These findings are consistent with those in the present study, suggesting that the small size of the pilot study may explain the discrepancy.

Although some studies[9,11] demonstrated a relationship between blood and cerebrospinal fluid Aβ levels, several studies[8–10] failed to show a relationship. A lack of cerebrospinal fluid data can be considered a limitation of the present study. Furthermore, a longitudinal follow-up study using amyloid positron emission tomography in a larger sample of patients will be needed to confirm the present findings.

CONCLUSION

The serum Aβ40/Aβ42 ratio was significantly higher in patients with MDD than in controls in all age groups, including younger individuals. This finding suggests that changes in amyloid metabolism may be affected in depression, and it may address the question of why even early-onset depression is a risk factor for developing AD.

Drug names: imipramine (Tofranil and others), lithium (Lithobid and others), paroxetine (Paxil, Pexeva, and others), valproic acid (Depakene, Stavzor, and others).

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