Plasma Aβ40 and Aβ42 and Alzheimer's disease

Relation to age, mortality, and risk

R. Mayeux, MD; L.S. Honig, MD; M.-X. Tang, PhD; J. Manly, PhD; Y. Stern, PhD; N. Schupf, PhD; and P.D. Mehta, PhD

Abstract—*Background:* Plasma amyloid β-peptide (Aβ) 40 and Aβ42 levels are increased in persons with mutations causing early-onset familial Alzheimer's disease (AD). Plasma Aβ42 levels were also used to link microsatellite genetic markers to a putative AD genetic locus on chromosome 10 and were observed in patients with incipient sporadic AD. *Methods:* The authors measured plasma Aβ40 and Aβ42 levels using a sandwich ELISA after the initial examination of 530 individuals participating in an epidemiologic study of aging and dementia. Participants were examined at 18-month intervals, and plasma Aβ40 and Aβ42 levels were repeated in 307 subjects 3 years after baseline. *Results:* Compared with individuals who never developed AD, patients with AD at baseline and those who developed AD during the follow-up had significantly higher Aβ42, but not Aβ40, plasma levels. The risk of AD in the highest quartile of plasma Aβ42 was increased by more than twofold over that in the lowest quartile. The highest plasma Aβ42 levels were observed in patients with AD who died during the follow-up. Plasma Aβ42, but not Aβ40, levels decreased over time in patients with newly acquired AD. *Conclusions:* Plasma Aβ40 and Aβ42 increase with age and are strongly correlated with each other. Plasma Aβ40 and Aβ42 levels are elevated in some patients before and during the early stages of AD but decline thereafter. High plasma Aβ42 levels may also be associated with mortality in patients with AD.

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Amyloid β-peptide (Aβ) peptide deposition in the brain and blood vessels is a distinctive manifestation of Alzheimer's disease (AD).[1] Two peptides of 40 and 42 amino acids in length (Aβ40 and Aβ42) are derived from the larger β-amyloid precursor protein (βAPP), which is expressed throughout the body. The Aβ peptides have also been detected in CSF, urine, plasma, and skin.[2-7] Aβ42 is increased in the plasma of affected and unaffected family members with mutations in presenilin 1 and 2 and the APP that cause early-onset familial AD.[8] Plasma Aβ40 and Aβ42 levels represent a heritable trait that has been used in a linkage analysis of chromosome 10 to AD, suggesting that variant forms of a gene may be associated with elevated levels of Aβ42.[9,10] The source of Aβ40 and Aβ42 in plasma is unknown, however. The brain has been considered the origin of deposited Aβ in the brain of patients with AD, but peripheral sources such as blood may also be important.[11]

Compared with age-matched control subjects, Aβ40 and Aβ42 levels are significantly increased in the plasma of patients with Down syndrome and further increased in the presence of dementia or the ϵ4 variant of *APOE*.[12] We previously reported an increase in plasma Aβ42 among individuals with incipient AD in a previous study.[6] Our results suggested that plasma Aβ42 might be a biological risk factor for AD but was not useful as a diagnostic test. The current study was designed to extend the risk analysis of plasma Aβ42 levels with incident AD and to determine whether plasma Aβ42 levels change with disease progression, age, or other characteristics.

Methods. *Study population.* Plasma Aβ40 and Aβ42 and clinical data were obtained from 530 individuals randomly selected from 2,126 Medicare recipients, 65 years and older, residing in northern Manhattan in New York City and participating in a study of aging and dementia. The sampling procedures for the parent study have been described elsewhere.[13] Participants underwent an in-person structured interview of health, a physical and neurologic examination, and a neuropsychological battery at the time of study entry, which was repeated at approximately 18-month intervals. Only individuals who completed at least one follow-up were included in the analyses. The Columbia University Institutional Review Board reviewed and approved this project. All individuals provided written informed consent.

Clinical assessments. Physicians completed standardized medical and neurologic histories and examinations. With use of a standard protocol, standing body weight to the nearest 0.1 kg with a balance scale (Scale-Tronix, Wheaton, IL) and height without shoes to nearest 0.5 cm were measured using a stadiometer (GNP,

From the Taub Alzheimer's Disease Research Center (Drs. Mayeux, Honig, Tang, Manly, Stern, and Schupf), Gertrude H. Sergievsky Center (Drs. Mayeux, Tang, Manly, Stern, and Schupf), Departments of Neurology (Drs. Mayeux, Honig, Manly, and Stern) and Psychiatry (Drs. Mayeux and Stern), and Divisions of Epidemiology (Dr. Mayeux) and Biostatistics (Dr. Tang), School of Public Health, Columbia University, New York, and Laboratory of Epidemiology (Dr. Schupf) and Department of Immunology (Dr. Mehta), Institute for Basic Research in Developmental Disabilities, Staten Island, NY.

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Address correspondence and reprint requests to Dr. R. Mayeux, Gertrude H. Sergievsky Center, Columbia University, 630 W. 168 St., New York, NY 10032; e-mail: rpm2@columbia.edu

Geneva, Switzerland) to calculate body mass index (BMI = weight/height^2).

The neuropsychological test battery, previously validated for this geographic area,[14,15] was given in either Spanish or English. The battery consisted of the orientation subtest from the modified Mini-Mental State Examination,[16] the Boston Naming Test,[17] the Controlled Word Association Test,[18] category naming, the Complex Ideational Material and Phrase Repetition Subtests of the Boston Diagnostic Aphasia Evaluation,[19] the Abstract Reasoning and Similarities Subtests from the Wechsler Adult Intelligence Scale–Revised,[20] the nonverbal Identities and Oddities Subtest of the Mattis Dementia Rating Scale,[21] the Rosen Drawing Test,[22] the matching version and the multiple-choice version of the Benton Visual Retention Test,[23] and the Selective Reminding Test.[24]

After each clinical assessment, a group of physicians and neuropsychologists reviewed the data and reached a consensus regarding the presence or absence of dementia[25] using published criteria for probable and possible AD.[26] Severity of AD was rated using the Clinical Dementia Rating Scale (CDR).[27] The consensus group was shielded from the plasma Aβ levels.

Ethnic group. At baseline, ethnic group was documented by self-report using the format of the 1990 US Census.[28] All individuals were first asked to indicate their racial group and then whether or not they were of "Hispanic origin."

Plasma lipids. Fasting plasma total cholesterol and triglyceride levels had also been determined from plasma ascertained at baseline using standard enzymatic techniques. High-density lipoprotein (HDL) cholesterol was determined after precipitation of ApoB-containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol levels were calculated using the formula of Friedewald et al.[29] This was done to examine the putative relation between alterations in cholesterol and Aβ levels in AD.[30]

APOE *genotype.* Genotypes were obtained by amplification of genomic DNA with PCR subjected to *Cfo*I restriction analysis using *APOE* primers and conditions similar to those described by Hixson and Vernier[31] and modified by Maestre et al.[32]

Plasma Aβ40 and Aβ42. Plasma obtained at baseline and follow-up was stored within 2 hours after collection at −70 °C. Aβ40 and Aβ42 levels were measured using a combination of monoclonal antibody 6E10 (specific to an epitope present on 1 to 16 amino acid residues of Aβ) and rabbit antibodies specific for Aβ40 (R162) and Aβ42 (R165) in a double-antibody sandwich ELISA.[33,34] The detection limit for this assay was 5 pg/mL for Aβ40 and 10 pg/mL for Aβ42. Previously, we had established that the test–retest reliability of the measurement of plasma Aβ40 and Aβ42 was excellent (Cronbach's α coefficient = 0.91).[6]

Data analysis. Continuous measures were compared across groups using Student's *t*-test, and categorical variables were compared using the χ^2 test. We subtracted the value of the plasma Aβ levels at baseline from that acquired 3 years later to estimate the change in levels over time. The change was compared using analysis of variance. Correlations between variables were completed using Pearson's correlation coefficient. Log transformation was used for continuous variables that appeared skewed. Univariate regression models were used to determine the relation between AD and plasma Aβ levels, and multivariate regression models were used to adjust for potential confounders. Finally, we used Cox regression to examine the rate ratio for AD associated with plasma Aβ42 levels divided into quartiles, in which the lowest quartile was used as the reference. For these analyses, we used duration of follow-up from the baseline measurement of plasma Aβ levels as the time-to-event variable. In subsequent analyses, we adjusted for age, education, *APOE* genotype, and BMI. All analyses were conducted using SPSS for Windows (version 10.1.3; Chicago, IL).

Results. At the baseline assessment, there were 79 (14.9%) patients with clinically diagnosed AD (CDR ≥ 1.0) among the 530 individuals in the study. The remaining 451 individuals were free of dementia (400 were CDR = 0 and 51 CDR = 0.5). Over the subsequent 5 years, 65 (16.3%) of the 400 without dementia and 21 (41.2%) of those with mild impairment (CDR = 0.5) developed AD (CDR = 1).

Compared with those who remained healthy, there were more African Americans and Hispanics than whites and more women than men with AD at baseline (table 1). Patients with AD were also older, less well educated, and more likely to have an *APOE*-ϵ4 allele than those without dementia. Over the follow-up period, more African Americans and Hispanics than whites and more women than men developed AD (see table 1). Individuals who developed AD were more likely to be older, less well educated, and more likely to have an *APOE*-ϵ4 allele than those who remained free of dementia. BMI was lower among the patients with AD at baseline than among newly diagnosed patients with AD or control subjects (see table 1).

Plasma Aβ40 and Aβ42 levels were correlated ($r = 0.22$, $p = 0.001$), and both increased with age (Aβ40 $r = 0.23$, $p < 0.001$; Aβ42 $r = 0.15$, $p < 0.001$). Aβ40, but not Aβ42, levels were inversely related to serum cholesterol and HDL levels ($r = -0.12$, $p = 0.005$, for both). Aβ42, but not Aβ40, level was inversely related to BMI ($r = -0.1$, $p = 0.05$). Neither Aβ40 nor Aβ42 levels differed by the presence or absence of an *APOE*-ϵ4 allele.

The initial Aβ40 and Aβ42 levels differed significantly in those individuals with AD at baseline compared with those without dementia (see table 1). More importantly, Aβ40 and Aβ42 levels were significantly higher in those who subsequently developed AD over the follow-up period (see table 1). The baseline Aβ40 levels, but not the Aβ42 levels, differed between those with CDR = 0 and those with CDR = 0.5 (Aβ40 131.5 [52.8; SD] vs 152.6 [94.8] pg/mL, $p = 0.05$; and Aβ42 61.3 [40.8] vs 69.5 [31.9] pg/mL, $p = 0.2$). However, regardless of the initial CDR, those who subsequently developed AD had higher baseline Aβ42 than those who never developed AD (Aβ42 CDR 0 = 77.4 [66.5], CDR 0.5 = 73.8 [31.9] vs controls 58.8 [32.9]; F = 14.1, $p = 0.0001$).

Because the distributions of Aβ40 and Aβ42 levels were skewed, the comparison was repeated using log transformations of Aβ40 and Aβ42 levels, and all of the associations with newly acquired AD described above remained significant. However, with multivariate analysis of covariance adjusting for age, BMI, and Aβ40 level, only Aβ42 levels remained significantly different when comparing those who never developed AD with those who developed AD over the follow-up period. In contrast, there were no significant differences in the Aβ40 level across the groups in the adjusted analysis. We also found no differences in the plasma Aβ40 and Aβ42 levels by disease severity using either the first or the last CDR rating. However, only two individuals had CDR ratings that exceeded 2, which reflects the fact that most patients had only mild disease.

Compared with the lowest quartile of plasma Aβ42 level at baseline, the unadjusted rate ratio for AD was significantly increased for each successive quartile after the second quartile (table 2). This association did not change in a multivariate Cox regression model that included Aβ40 level, age, BMI, education, and *APOE*-ϵ4. The figure shows the cumulative proportion of affected individuals within each quartile of plasma Aβ42. Only the upper two quartiles differed significantly from the lowest quartile, though the risk did increase for each quartile.

The baseline Aβ42 plasma level was also consistently and significantly higher among those individuals who developed AD at any time point during the follow-up than among those who never developed AD after 5 years of

Table 1 *Baseline demographics by final diagnoses*

Demographics, n = 530	AD at baseline	AD at follow-up	Nondemented elderly*
No. (%)	79 (14.9)	86 (16.2)	365 (68.9)
Mean (SD) age,†	83.2 (7.9)	79.3 (6.6)	75.5 (5.9)
Mean (SD) education,†	6.4 (4.2)	6.8 (4.5)	9.0 (4.6)
Gender,‡ women %	86.1	79.1	66.6
African American, %	15.7	16.8	67.5
Caribbean Hispanic, %	17.5	19.7	62.8
White, %	6.6	7.6	85.8
APOE-ε4 present,§ %	39.2	32.1	26.7
BMI (SD)§	25.7 (4.9)	27.4 (6.2)	27.5 (5.8)
Mean (SD) cholesterol, mg/dL	198.1 (42.3)	196.0 (41.4)	201.2 (40.8)
Mean (SD) Aβ40,§‖ pg/mL	153.6 (46.7)	136.2 (46.7)	133.3 (61.9)
Mean (SD) Aβ42,†§¶ pg/mL	68.7 (24.2)	76.5 (59.8)	58.8 (32.9)
Mean (SD) Aβ42/Aβ40*§	0.49 (0.23)	0.61 (0.53)	0.48 (0.3)

Note that for ethnic groups, the percentages reflect within-group proportions. African Americans do not include Hispanics. Hispanics are exclusively from the Caribbean Islands and Central and South America. Whites are of Eurasian ancestry and not Hispanic.

*Individuals who remained free of dementia throughout the follow-up period.
†$P < 0.001$.
‡$P < 0.01$.
§$P < 0.05$.
‖Linear trend, $P < 0.05$.
¶Linear trend, $P < 0.001$.

AD = Alzheimer's disease; BMI = body mass index; λAβ = amyloid β-peptide.

follow-up (mean Aβ42 levels for controls over the entire period 58.8 pg/mL, AD after 2 years of follow-up 77.1 pg/mL, AD after 4.1 years of follow-up 74.5 pg/mL; F = 6.04, $p = 0.003$). Thus, the average plasma Aβ42 levels were consistently elevated among those who subsequently developed AD compared with those who remained dementia-free.

We were able to obtain repeat blood samples in only 307 (58%) of the 530 individuals. This was due in part to mortality among 157 (29.6%) of the participants. Nonetheless, the correlation between the initial and subsequent plasma Aβ40 and Aβ42 levels was high (0.979 and 0.963, respectively). The change in overall mean Aβ40 levels differed slightly, but significantly, increasing over time (2.44 pg/mL; 95% CI 0.9 to 3.9). There was no significant change in Aβ42 level over time (−0.009 pg/mL; 95% CI −0.83 to 0.82), but in comparison there were significant differences in plasma Aβ42 levels among the different groups over time. Among controls that remained dementia-free, the average difference over the 3 years was 0.25 pg/mL, for prevalent AD the difference was −0.75 pg/mL, whereas the difference among patients with incident AD was −3.02 pg/mL (F = 4.2, $p = 0.02$). This difference was significant. Thus, the average decline in plasma Aβ42 levels was 1.006 pg/mL/year in patients with newly acquired AD.

We found that baseline plasma Aβ40 and Aβ42 levels were significantly higher among those who died before the final assessment (table 3). Specifically, those individuals with AD who subsequently died had higher baseline Aβ42 levels than those individuals without AD, those with AD at

Table 2 *Rate ratio of AD by plasma Aβ42 levels as quartiles*

Quartiles of Aβ42, pg/mL	No. at risk	AD, no. (%)	RR (95% CI)*	RR (95% CI)†
≤36.97	124	19 (15.3)	1.0 ref.	1.0 ref.
36.97–60.2	116	19 (16.4)	1.3 (0.7–2.4)	1.1 (0.6–2.1)
60.2–84.15	102	21 (20.6)	1.9 (1.1–3.6)‡	1.9 (1.0–3.7)‡
≥84.15	109	27 (24.8)	2.4 (1.3–4.3)§	2.5 (1.3–4.8)§

Note that prevalent AD is omitted from this analysis of disease risk by baseline Aβ42 levels. The time-to-event was duration of follow-up from the baseline evaluation. All subjects were dementia-free at that time.

*Unadjusted.
†Adjusted for age, education, Aβ40 level, *APOE* genotype, and body mass index.
‡$P = 0.05$.
§$P < 0.006$.

AD = Alzheimer's disease; Aβ = amyloid β-peptide; RR = rate ratio.

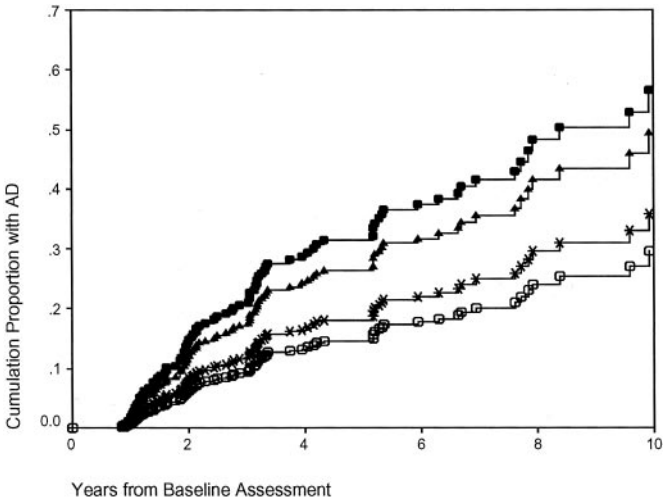

Figure. Risk of Alzheimer's disease (AD) by quartiles of amyloid β-peptide (Aβ42) plasma levels at baseline. This graph depicts the cumulative proportion of individuals developing AD over the entire period of follow-up by the plasma Aβ42 level at the baseline or initial visit. Quartiles of plasma Aβ42 are identified as follows: filled circles = >84.15 pg/mL; triangles = 84.15 to 60.2 pg/mL; asterisks = 60.2 to 36.97 pg/mL; open circles = ≤36.97 pg/mL.

baseline, and patients who developed AD and survived. The analysis was repeated using multivariate analysis of covariance adjusting for age, BMI, and baseline plasma Aβ40 level, and the difference remained significant. Plasma Aβ40 levels did not differ significantly in those who survived with or without AD and those who did not in the multivariate analysis. The unadjusted analysis was repeated using log transformation of the values for plasma Aβ40 or the Aβ42 levels, and the differences remained statistically significant.

Discussion. Compared with elderly without AD, patients with AD and individuals who developed AD over the follow-up period had higher plasma Aβ40 and Aβ42 levels at the beginning of the study. Plasma Aβ40 and Aβ42 levels were also higher in patients with AD at baseline compared with controls, though the differences were smaller. With use of the lowest quartile as the reference group, individuals in the upper two quartiles of plasma Aβ42 were at twice the risk of developing AD over the follow-up period. As a group, plasma levels of Aβ40 and Aβ42 drawn 3 years apart did not change significantly, but there was a significant decline in plasma Aβ42 levels in patients with newly acquired AD compared with those with prevalent AD or with controls. Over the study period, both plasma Aβ40 and Aβ42 levels were higher among those participants who died during the follow-up period than among those who survived. However, the multivariate analysis showed that baseline Aβ42 levels were higher in patients with recent onset of AD who died compared with those who survived with or without AD. This work extends our previous study, pointing out that differences in plasma level are related to age, BMI, and duration of time after the diagnosis. It also shows that the risk of AD may remain increased for those individuals with elevated plasma β42 over nearly 10 years.

Mutations in the genes that cause early-onset, familial forms of AD increase the extracellular concentration of Aβ42, which may augment Aβ deposition in the form of plaques in the brain.[35] This has led to the hypothesis that cerebral Aβ deposition is an essential early event in the pathogenesis of all forms of AD. Support for this hypothesis has come from the observation that plasma Aβ40 and Aβ42 levels were found to be higher in family members with mutations in presenilin 1 and the APP than among family members without the mutation.[8] We previously reported that plasma Aβ42, but not Aβ40, levels were increased among patients with incipient AD regardless of their *APOE* genotype in a small study from this same community.[6] Though patients with Down syndrome have higher plasma Aβ40 and Aβ42 levels due to the trisomy involving the region containing the APP,[36] even higher levels are found among pa-

Table 3 *Relation of plasma Aβ40 and Aβ42 levels, diagnosis, and vital status at last follow-up*

Group	Status*	No.	Age†	Aβ40, pg/mL	Aβ42, pg/mL
AD baseline	Alive	32	81.3 (7.5)	143.9 (40.6)	66.3 (23.6)
	Dead	45	84.6 (7.9)	160.4 (49.9)	70.3 (24.7)
Nondemented elderly	Alive	277	74.8 (5.6)	122.1 (39.7)‡	57.6 (33.7)
	Dead	88	77.4 (6.6)	168.3 (96.9)	62.8 (30.1)
AD follow-up	Alive	63	78.2 (5.6)	128.9 (45.8)	67.6 (49.8)§
	Dead	23	82.4 (8.1)	155.9 (45.0)	101.2 (77.1)

Comparisons are between participants who were alive or dead at the final assessment. Log-transformed values also differed significantly. Values in parentheses are SD.
*Status refers to the vital status at final assessment.
†Both nondemented elderly and patients with AD who died were significantly older than those surviving.
‡$P < 0.001$, comparing nondemented elderly follow-up alive vs dead.
§$P < 0.01$, comparing AD follow-up alive vs dead.

Aβ = amyloid β-peptide; AD = Alzheimer's disease.

tients who became demented.[12,37] It is not clear whether the *APOE* genotype influences plasma Aβ40 and Aβ42, because there are opposing reports.[12,37] Aβ40 and Aβ42 levels in plasma represent a heritable trait[9] that has been used as a phenotype in a genetic linkage analysis[10] that showed genetic linkage to markers on chromosome 10.

Do plasma Aβ42 levels represent a potential biological risk factor for AD? Our study has indicated that the answer to this question is complex. First, plasma Aβ40 and Aβ42 levels show some degree of overlap between elderly individuals who eventually develop AD and those who remained healthy, as would be expected with any risk factor. Second, we demonstrated that the measurement of plasma Aβ42 levels would need to be done at a point well before the onset of disease and thus could be used in the detection of individuals at higher-than-average risk. Careful inspection of the figure suggests that differences in frequency of AD by plasma Aβ42 levels emerge only after 2 to 3 years of follow-up. Therefore, a cross-sectional comparison of patients with established diagnoses of AD and control subjects would be unlikely to show a difference in the mean levels of either peptide. Third, the validity of plasma Aβ42 levels as a risk factor will be difficult to establish without more extensive longitudinal data because the highest levels were observed among individuals in the earliest stages of disease when the specificity of diagnosis is low. Therefore, high-risk individuals will need follow-up to a point at which the diagnostic specificity is greater. Although we observed little difference in the levels over a 3-year period, it may be necessary to complete repeated testing over a longer interval to examine changes in plasma levels with regard to disease course. Fourth, the highest Aβ40 and Aβ42 were found in those patients who died during the follow-up period, again implying that longitudinal, not cross-sectional, studies will be required to determine their usefulness in assessing disease risk. An alternative explanation is that the association with mortality implicates plasma Aβ40 and Aβ42 levels as indicators of prognosis.

We believe that neither plasma Aβ40 nor Aβ42 levels will be useful in the diagnosis of AD. Our limited results with repeated samples indicate that the plasma levels of Aβ42 begin to decrease soon after the diagnosis of AD has been established, which has been observed by others.[38] Exactly when plasma levels begin to decrease is uncertain. In contrast, CSF concentrations of Aβ42 have been used successfully when combined with other biochemical markers such as τ in the diagnosis of probable AD.[39,40] Aβ42 in the CSF is lower in patients with the disease than in controls. CSF concentrations of Aβ42 are increased early in the disease and decrease over time.[41] Previous studies examining the role of plasma Aβ40 and Aβ42 levels have shown little or no value in the diagnosis of AD.[5,42]

We found an inverse relation between Aβ40 levels and cholesterol and HDL in plasma. There may well be a relationship between Aβ deposition in brain and cholesterol, but it has not been observed in plasma.[43,44] We could not identify an association between increased plasma Aβ and elevated serum cholesterol.[45] The studies of families with early-onset AD caused by mutations and the recent linkage of families with late-onset disease to chromosome 10 implicate exceptionally high plasma Aβ42 levels as part of the phenotype of a form of familial AD. Thus, an alternative possibility is that plasma Aβ42 may be increased only in a subset of individuals who develop AD. If the elevation in Aβ42 is a phenotypic marker in some, but not all, patients, then the search for the genes associated with higher levels will be extremely important because new metabolic pathways may be revealed. The persistence of the elevation in the patients studied here, the sparse number of individuals with elevated levels, and their death over the follow-up would suggest a moderately aggressive form of the disease that can be either genetic or environmental.

Aside from studies of early-onset familial AD,[46,47] there have been no reports suggesting that elevated levels of circulating plasma Aβ40 or Aβ42 are associated with mortality. It is intriguing to speculate that in some individuals with AD, higher levels of Aβ40 and Aβ42 may reflect a more advanced stage of disease or a more aggressive form of AD. The only animal model that has been studied is the senescence-accelerated mouse, which has a short life span and shows early signs of aging.[48] However, the amyloid deposition is systemic, affecting numerous systems in the body.

The source of Aβ40 and Aβ42 in plasma is unknown. Aβ is derived from proteolytic cleavage of the APP.[1] APP is produced by a variety of cell types in the brain and elsewhere, but the origins of Aβ brain deposits in AD and deposits in the cerebral vessels are uncertain. Amyloid deposits in cerebral vessels may be derived from circulating Aβ.[49] Some have suggested that the source of parenchymal cerebral amyloid deposits may originate in the periphery.[50] Platelets contain high levels of membrane-associated and soluble forms of APP, which, when cleaved, can release Aβ.[51-53] Platelets may also be the source of Aβ detected in whole blood[54] because Aβ, like APP, is also released upon platelet activation.[52,55] Aβ and APP formation and subsequent release from human platelets may be regulated by different multiple signal transduction mechanisms.[11] Knowledge of these mechanisms could provide a key to the pathogenesis of AD.

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R. Mayeux, L. S. Honig, M.-X. Tang, et al.

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