CSF Aß 42 levels correlate with amyloid-neuropathology in a population-based autopsy study

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Neurology 2003;60;652-656

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Abstract—*Objective:* To investigate the relationship of amyloid neuropathology to postmortem CSF Aβ 42 levels in an autopsy sample of Japanese American men from the population-based Honolulu–Asia Aging Study. *Methods:* In 1991, participants were assessed and diagnosed with dementia (including subtype) based on published criteria. At death CSF was obtained from the ventricles. Neuritic plaques (NP) and diffuse plaques in areas of the neocortex and hippocampus were examined using Bielschowsky silver stains. Cerebral amyloid angiopathy (CAA) was measured by immunostaining for β4 amyloid in cerebral vessels in the neocortex. Neuropathologically confirmed AD was diagnosed using Consortium to Establish a Registry for Alzheimer's Disease criteria. In 155 autopsy samples, log transformed linear regression models were used to examine the association of NP and CAA to Aβ 42 levels, controlling for clinical dementia severity, time between diagnosis and death, age at death, brain weight, hours between death and collection of CSF, education, and *APOE* genotype. *Results:* Higher numbers of NP in the neocortex (p trend = 0.001) and in the hippocampus (p trend = 0.03) were strongly associated with lower levels of Aβ 42. Individuals with CAA had lower Aβ 42 levels (β coefficient = −0.48; 95% CI −0.9, −0.1). Compared to participants with a diagnosis of clinical dementia, those with pathologically confirmed AD had lower Aβ 42 levels (β coefficient = −0.74; 95% CI −1.4, −0.1). *Conclusion:* The current study suggests that lower Aβ 42 levels reflect neuropathologic processes implicated in amyloid-related pathologies, such as NP and CAA.

NEUROLOGY 2003;60:652–656

At present, a definitive diagnosis of AD depends on finding neuritic plaques (NP) in the brain of an individual with a clinical diagnosis of progressive dementia.[1] Together with advanced imaging techniques and a clinical examination, low Aβ 42 combined with high tau levels in CSF have been proposed as biochemical markers that add some value in early clinical diagnosis.[2-4] Aβ 42 is the core peptide that accumulates in NP and has been implicated in the pathogenesis of cerebral amyloid angiopathy (CAA). CAA is present in 62 to 95% of patients with AD and consistently in Down syndrome, but it is also found in nondemented elderly individuals.[5,6]

Thus, we examined CSF Aβ 42 levels in relation to amyloid plaques and CAA in a population-based autopsy sample of clinically demented and nondemented Japanese American men. We also investigated the relationship of CSF Aβ 42 levels to clinicopathologic AD groups and *APOE* ϵ4 allele.

Methods. The autopsy sample is from a cohort of Japanese American men participating in the population-based Honolulu–Asia Aging Study (HAAS). The HAAS began in 1991 as a supplement to the Honolulu Heart Program Study to investigate the determinants of dementia. From 1991 to 1993 (examination 4), 3,734 individuals were examined, and were subsequently reexamined in 1994 through 1996 (examination 5) and in 1997 through 1999 (examination 6). All participants were eligible for the autopsy substudy; cases of dementia were preferentially followed up to ensure adequate sample size for comparisons of cases to controls. The autopsy sample is similar to the nonautopsied decedents from the cohort.[7,8] The institutional review board of the University of Hawaii approved the study, and informed consent for the HAAS study and the autopsy study was obtained from the study participants, or from a proxy in the case of dementia.

Dementia was diagnosed in a three-step procedure described in detail elsewhere.[8,9] Briefly, diagnosis was based on neuropsychologic testing, a neurologic examination, an informant interview, and neuroimaging (in 86% of cases). All recognized subtypes of dementia were considered, and the Clinical Dementia Rating (CDR) index was assigned in the diagnostic consensus conference that included a neurologist and at least two other study investigators.

At autopsy, tissue from four areas of the neocortex (middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, and occipital cortex) and two areas of hippocampus (CA1 and subiculum) were taken. Bielschowsky and Gallyas silver stained sections were prepared to visualize amyloid plaques and neurofibrillary tangles (NFT). Samples were evaluated by one of three neuropathologists who participated in a training session aimed at standardization of reading techniques. The evaluation was done blinded to clinical information.

Both diffuse plaques and NP were counted. Senile plaques (SP) included NP and diffuse plaques. NP were defined as plaques containing silver-positive neurites; diffuse plaques were those without neurites. Five fields standardized to 1 mm^2 were examined for each of the four neocortical and two hippocampal areas. The field with highest count was taken to represent the brain area. Counts for NP and NFT were calculated by averaging across the four neocortical or two hippocampal areas. Results were recorded as NP per square millimeter and were truncated at 17/mm^2.[10] There was no upper limit for NFT counts.

To detect CAA in parenchymal arteries and arterioles, four sections from the neocortex were immunostained with βA4 amyloid (clone 10D5, Athena Neurosciences, San Francisco, CA).[11] If

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Received July 2, 2002. Accepted in final form October 25, 2002.

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all vessels within all four areas were nonreactive the sample was designated CAA absent. A grade of mild CAA was given to men with only one or two βA4-positive vessels in one or more areas. Men with three to five positive vessels in at least one area received an overall grade of moderate, and those with greater than five positive vessels were designed severe.

Postmortem ventricle CSF was obtained at death and stored at −70 °C. Aβ 42 was measured using a special high-sensitivity version of sandwich ELISA [INNOTEST β-amyloid(1-42), Innogenetics, Ghent, Belgium] constructed to specifically measure Aβ 42, as described previously.[12,13] The lowest detectable level was 7 pg/mL.

To check whether contamination of CSF with blood at the time of collection affected CSF Aβ 42 levels, all CSF samples were evaluated by visual inspection after centrifugation. Blood contamination was graded as none (clear CSF), mild-moderate (mild to moderate pink-reddish CSF), and marked (red CSF). There was no difference in the mean CSF Aβ 42 levels among CSF samples with no (46%, 93.5 ± SD 124 pg/mL), mild-moderate (25%, 118 ± SD 210 pg/mL), and marked (29%, 91.2 ± SD 132 pg/mL) contamination with blood (Kruskal-Wallis one-way analysis of variance $p = 0.16$).

Analytical sample. Of a total of 253 autopsy cases, complete data were available on 170. There were 19 samples with missing data on Aβ 42, and 64 specimens had not been evaluated microscopically by the time the Aβ 42 measurements were completed. We found a strong correlation between Aβ 42 and the interval between death and CSF collection (Spearman rho = −0.5; $p < 0.001$). We excluded 15 individuals with an interval of more than 24 hours; because there are no data on Aβ 42 aggregation or degradation over time, this remains an arbitrary cutpoint. This gave us an analytical sample of 155 men. Compared to the total autopsy sample, the 155 men were proportionally more demented (39% compared to 30%) and had a shorter postmortem collection interval (on average 11.4 hours compared to 28.9 hours). The total autopsy sample was similar to the nonautopsied decedents except they were older, and by design included more men who were clinically diagnosed with dementia before death.

In the analytical sample the mean time interval of specimen collection after death was 11.5 (±5.9) hours. Postmortem interval (PMI) was not different by dementia severity. Compared to nondemented subjects with a mean age- and education-adjusted PMI of 11.9 hours, mildly demented subjects had a PMI of 10.7 hours (p value = 0.38), and severely demented subjects had a PMI of 10.8 hours (p value = 0.38).

Mean age at death was 85.4 (±5.6) years. There were 95 clinically nondemented men (61.3%) and 60 clinically demented men, including 30 cases of probable and possible AD, 22 cases of vascular dementia (VaD), and 8 cases of other dementias, including PD and Lewy body disease, trauma plus dementia, and dementia of undetermined cause. Interval between last diagnosis and death was on average 3.3 years (range 0 to 9 years).

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria were used for diagnosis of AD.[1] These criteria are based on semiquantitative assessment of NP. Three illustrations representing sparse, moderate, and frequent plaque densities per square millimeter are used as guides for comparison with the microscopic case being assessed. In individuals older than 75 years at death with a clinical history of dementia, a match with the frequent NP illustration confers a neuropathologic diagnosis of definite AD, and the diagnosis of probable AD is made when the case matches the moderate frequency illustration. A maximum NP count of $\geq 17/mm^2$ was used to meet CERAD requirements for definite AD, and a count of at least $4/mm^2$ was used to meet CERAD requirements for probable AD.[8] Among all clinically demented subjects (n = 60), 48% (n = 29) received a neuropathologic diagnosis of probable or definite AD. A possible neuropathologic diagnosis of AD was given to individuals without clinical dementia and with four NP or more. Accordingly, 23% (n = 22) of the nondemented participants met possible AD CERAD criteria.

Analysis. Counts for NP and SP were divided into four groups: zero plaques and, among those with plaques, tertiles were created. Cutpoints for NP and SP are presented in table 1. The strata of zero plaques served as a reference. The association of Aβ 42 levels to NP and SP was examined separately for the neocortex and hippocampus. Aβ 42 was transformed into a log scale to obtain normality. For all our analyses, we used a general linear regression model. We adjusted for age at death, CDR score at time of diagnosis, interval between diagnosis and death, education, and *APOE* ϵ4 allele[14] (presence or absence of the ϵ4 allele). To control for Aβ degradation, we adjusted for the interval from time of death to collection of CSF (in hours). We also controlled for total brain weight (in grams). Fifty-seven men (36%) had severe CAA, 11 (7.1%) had moderate CAA, and 13 (8.4%) had mild CAA. To increase statistical power we dichotomized the CAA variables as CAA present (mild, moderate, or severe) and CAA absent. For the analysis on NP, we adjusted for CAA, and vice versa we adjusted for NP.

The model was examined three ways: for the total sample, stratified by dementia status, and stratified by *APOE* ϵ4 allele. To look at the specificity of the association between Aβ 42 and amyloid pathology, we also examined the association of NFT to Aβ 42.

Results. Levels of Aβ 42, NP count, and CAA by sample characteristics are given in table 2. Aβ 42 levels ranged from 7 pg/mL to 1,088 pg/mL with a median of 58 pg/mL (interquartile range 14 to 116).

Neuritic plaques. Increasing NP count was associated with a significant decrease in Aβ 42 levels after adjusting for all covariates (see table 1, figure). The association of Aβ 42 to SP in the neocortex and hippocampus was similar (see table 1).

After removing the demented participants from our analysis (see the figure), there was still an inverse relationship with NP in the neocortex (β coefficient = −1.41; 95% CI −2.2, −0.6; p trend = 0.002) and in the hippocampus (β coefficient = −0.65; 95% CI −1.5, 0.2; p trend = 0.04).

Samples collected within 16 hours of death had higher Aβ 42 levels than those collected within 24 hours (see table 2). Among Aβ 42 samples collected within 16 hours, fully adjusted Aβ 42 means were 106.9 pg/mL for those with no neocortical NP (hippocampal NP = 83.4 pg/mL) and 34.8 pg/mL for those in the strata with the highest NP count (hippocampal NP = 38.6 pg/mL). Values for SP were comparable to the NP results.

Cerebral amyloid angiopathy. Individuals with CAA had significantly lower Aβ 42 levels (see table 1); individuals with severe CAA had lower levels of Aβ 42 than individuals with mild to moderate CAA or no CAA (p trend = 0.06). Those with CAA and NP had the lowest values (see table 1). After removing the demented participants, levels were still lower (β coefficient = −0.40; 95% CI −0.9, 0.1).

Neuropathologic diagnosis. Among individuals diagnosed as demented before death (n = 60), those with probable or definite pathologic AD (n = 29) had significantly lower adjusted means for Aβ 42 (table 3). Among clinically nondemented participants (n = 73), those with pathologically confirmed possible AD (n = 22) had lower Aβ 42 levels (see table 3).

The *APOE* ϵ4 allele did not modify the associations reported here, but there were too few ϵ4 carriers (n = 22) to draw a firm conclusion. We could not observe any relationship between CSF Aβ 42 levels and NFT (data not shown).

Discussion. In this well-assessed population-based autopsy study, we found a strong inverse association of postmortem CSF Aβ 42 with the number of NP and SP. Even in nondemented individuals a decrease in Aβ 42 reflected increasing plaque load. In addition, we observed that lower Aβ 42 levels were associated with CAA.

The strength of our study is the assessment of clinical and neuropathologic data in a population-based sample of nondemented and demented individuals. To our knowledge this is the first study to examine the association of lower CSF Aβ 42 levels, NP, and CAA. Several inpatient studies found a decrease in antemortem CSF Aβ 42 levels with AD, and with other dementia subtypes,[12,15-17] but these studies have not had confirming autopsies.

Despite the strengths of the current study, the one-point clinical dementia assessment and the mea-

Table 1 *Results of the association of Aβ42 with neuropathologic markers of AD*

Markers	N	Mean Aβ42 pg/mL	Log mean (95% CI)	*p* Trend
SP—Neocortex*†				
0 Senile plaques (SP)	64	70.8	4.25 (0 reference)	0.001
Low tertile (0.9–4.9)	19	50.1	−0.36‡ (−0.9, 0.2)	
Mid tertile (5.0–15.0)	34	37.8	−0.63 (−1.1, −0.1)	
High tertile (15.0–17.0)	38	27.8	−0.94 (−1.5, −0.4)	
SP—Hippocampus*†				
0 Senile plaques	80	64.5	4.17 (0 reference)	0.004
Low tertile (0.3–1.7)	25	39.7	−0.5‡ (−1.0, −0.0)	
Mid tertile (2.0–6.0)	25	26.3	−0.9 (−1.4, −0.4)	
High tertile (6.0–17.0)	25	36.1	−0.59 (−1.2, −0.03)	
NP—Neocortex*				
0 Neuritic plaques (NP)	72	73.6	4.3 (0 reference)	<0.0001
Low tertile (0.1–2.0)	28	33.2	−0.82‡ (−1.3, −0.3)	
Mid tertile (2.0–6.5)	28	40.3	−0.62 (−1.1, −0.1)	
High tertile (6.5–17.0)	27	24.0	−1.13 (−1.7, −0.6)	
NP—Hippocampus*				
0 Neuritic plaques	85	56.4	4.0 (0 reference)	0.03
Low tertile (0.3–1.7)	25	42.4	−0.3‡ (−0.8, 0.2)	
Mid tertile (2.0–5.0)	24	41.5	−0.31 (−0.9, 0.2)	
High tertile (5.0–17.0)	21	29.4	−0.66 (−1.3, −0.1)	
Cerebral amyloid angiopathy (CAA)§				
No	74	60.6	0 (0 reference)	
Yes	81	37.3	−0.48‡ (−0.9, −0.1)	
NP/CAA groups‖				
No NP/no CAA	47	82.0	4.4 (0 reference)	
No NP/CAA present	14	81.3	−0.01‡ (−0.7, 0.6)	
NP present/no CAA	27	56.2	−0.38 (−0.9, 0.1)	
NP present/CAA present	67	26.4	−1.13 (−1.6, −0.7)	

* Adjusted for age at death, education, postmortem time interval until Aβ 42 measurement, *APOE* ε4, CAA, CDR, time for diagnosis until death, and brain weight.
† Includes NP and diffuse plaques.
‡ Adjusted difference between log mean levels of Aβ 42.
§ Adjusted for all covariates as described above, plus NP.
‖ All covariates as described above minus CAA.

CDR = Clinical Dementia Rating.

surement of Aβ 42 in postmortem CSF are limitations. Because there was a range of up to 9 years from the last clinical assessment until death, there remains the possibility that some nondemented individuals developed clinical symptoms of dementia before death. Demented participants will also have progressed. An ideal study design would include repeated antemortem clinical assessments and CSF samples coupled with an autopsy to address the added diagnostic value of Aβ 42.

The values of Aβ 42 differ between research laboratories. Our Aβ 42 levels were lower than in published lumbar premortem assessments,[18] most likely owing to a concentration difference in levels between Aβ 42 measured from ventricle CSF and lumbar CSF. CSF Aβ 42 levels are stable during freezing.[2] We found, however, a negative correlation between Aβ 42 levels and postmortem interval, suggesting some Aβ 42 degradation or aggregation. We tried to account for this by excluding those with a very long postmortem collection interval, and by controlling for postmortem interval.

Neither the mechanisms by which insoluble Aβ 42 accumulates in the extracellular spaces as NP or in cerebral vessels as CAA nor the relationship between that build-up and the levels of Aβ 42 in the CSF are very well understood. Derived from the transmembrane β-amyloid precursor protein (APP) in neurons, Aβ has two major forms: Aβ 40, a shorter, more soluble form; and Aβ 42, which is longer and more

Table 2 *Characteristics of participants according to CAA, NP counts, and mean of Aβ42 levels**

Characteristics	NP count				
	Percent with CAA	Neocortex, Median (IQR)	Hippocampus, Median (IQR)	Aβ42 mean†	*p* Value‡
Age, y					
<85	45	0 (0–1.9)	0 (0–2.6)	56.7	0.05
≥85	60	1.5 (0–5)	0 (0–2.4)	39.7	
Education, y					
≤6	48	0 (0–3.9)	0 (0–1.3)	88.7	0.007
>6	53	0.5 (0–4.2)	0 (0–2.6)	42.6	
Postmortem collection interval, h					
<8	61	0.3 (0–3.9)	0.3 (0–2.6)	99.4	<0.0001§
8–16	53	0.3 (0–6.8)	0 (0–3.9)	39.6	
>16	37	0.2 (0–3.8)	0 (0–1.3)	20.1	
APOE ε4 allele					
No	48	0.3 (0–3.9)	0 (0–1.7)	49	0.48
Yes	77	1.7 (0–6.8)	2.1 (0–7.4)	40.4	
Infarcts/lacunes					
No	51	1 (0–4.3)	0 (0–3.2)	49.6	0.57
1+	54	0 (0–3.9)	0 (0–2.4)	44.6	
CAA					
No	—	0 (0–0.2)	0 (0–0)	72.3	<0.0001
Yes	—	3.7 (1.0–8.1)	1.6 (0–4.9)	31.7	

* Adjusted for age at death, education, and time interval from death to specimen collection.
† Back transformed from the geometrical mean.
‡ For the relationship of Aβ 42 levels between groups.
§ *p* For trend in Aβ 42.

CAA = cerebral amyloid angiopathy; NP = neuritic plaques; IQR = interquartile range.

insoluble.[19] Whereas Aβ 40 is the major form of Aβ formed from APP, it forms amyloid fibrils less readily than Aβ 42. Thus, Aβ 42 is the major form deposited as insoluble plaques in the extracellular spaces of the cerebral cortex. Aβ 40 is the major form of amyloid deposited in the walls of leptomenigeal arteries in cerebral CAA.[19-21] Experimental studies have suggested that Aβ drains along very narrow, periarterial interstitial fluid (ISF) pathways in the gray matter to join the CSF at the surface of the brain.[22,23] In humans, the pattern of Aβ deposition in vessel walls follows that of ISF drainage patterns outlined by tracer experiments in animals, except that instead of entering the CSF in the subarachnoid

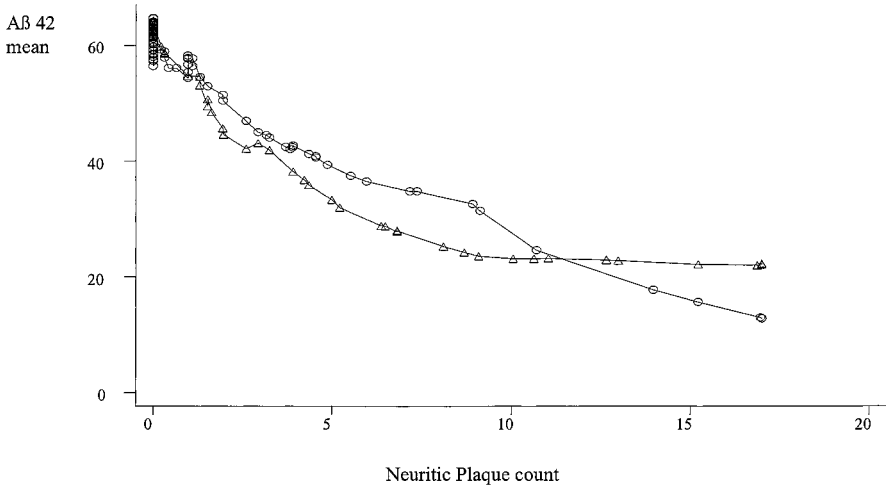

Figure. Predicted relationship of Aβ 42 levels and neuritic plaques in the neocortex stratified by dementia (adjusted for age at death, education, postmortem time interval until Aβ 42 measurement, APOE ϵ4, cerebral amyloid angiopathy, dementia severity, time from diagnosis until death, and brain weight). Circles = nondemented; triangles = demented.

Table 3 *Aβ42 by neuropathologic diagnosis*

Diagnosis	N	Mean Aβ42 pg/mL	Log mean (95% CI)
Neuropathologic AD vs rest of the clinically demented*			
Clinically demented	31	59.8	0 (reference)
CERAD probable/definite AD	29	28.3	−0.74† (−1.4, −0.1)
Neuropathologic AD vs rest of the clinically nondemented‡			
Nondemented	73	62.1	0 (reference)
CERAD possible AD	22	26.0	−0.87† (−1.4, −0.3)

* Adjusted for age at death, education, postmortem time interval until Aβ42 measurement, *APOE* ε4, dementia severity, time from diagnosis until death, and brain weight.
† Adjusted difference between log mean levels of Aβ42.
‡ All covariates as described above minus dementia severity.

CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

space, much of the Aβ remains in the vessel walls.[21,24] Thus, lower Aβ 42 levels in CSF may reflect increased deposition in NP and vessels, and diminished clearance into the CSF.[25] It is also possible that levels are altered because of plaque-related disturbances in the equilibrium between CSF Aβ 42 and plasma Aβ 42.[26] Factors controlling Aβ metabolism after its production, such as local clearance or clearance to plasma, may also influence CSF levels.[27]

The current study suggests that lower Aβ 42 levels reflect neuropathologic processes implicated in amyloid-related pathologies, such as NP and CAA.

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