Change in plasma A β peptides and onset of dementia in adults with Down syndrome

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ABSTRACT

Objective: To examine changes in levels of plasma amyloid- β (A β) peptides, A β 42 and A β 40, in relation to onset of Alzheimer disease (AD) in adults with Down syndrome (DS).

Methods: Plasma A β 42 and A β 40 were measured at initial examination and at follow-up in a community-based cohort of 225 adults with DS who did not have dementia at baseline and were assessed for cognitive/functional abilities and health status and followed at 14- to 20-month intervals. We used Cox proportional hazards modeling to estimate the cumulative incidence of AD by A β peptide change group (increasing, no change, or decreasing), adjusting for covariates.

Results: Sixty-one (27.1%) of the participants developed AD. At follow-up, a decrease in A β 42 levels, a decrease in the A β 42/A β 40 ratio, and an increase in A β 40 levels were related to conversion to AD. Compared with the group with increasing levels of A β 42, the likelihood of developing AD was 5 times higher for those whose plasma A β 42 levels decreased over follow-up (hazard ratio [HR] = 4.9, 95% confidence interval [CI] 2.1–11.4). Decreasing A β 42/A β 40 was also strongly related to AD risk (HR = 4.9, 95% CI 1.8–13.2), while decreasing A β 40 was associated with lower risk (HR = 0.4, 95% CI 0.2–0.9).

Conclusions: Among adults with DS, decreasing levels of plasma A β 42, a decline in the A β 42/A β 40 ratio, or increasing levels of A β 40 may be sensitive indicators of conversion to AD, possibly reflecting compartmentalization of A β peptides in the brain. *Neurology*® 2010;75:1639–1644

GLOSSARY

A β = amyloid- β ; AD = Alzheimer disease; APP = amyloid precursor protein; CI = confidence interval; DS = Down syndrome; HR = hazard ratio; MCI = mild cognitive impairment.

Amyloid- β (A β) plays a critical role in the development of Alzheimer disease (AD). A β peptides A β 40 and A β 42 are the 2 major species generated by sequential proteolytic cleavage by β and δ secretases of the amyloid precursor protein (APP).¹ Brain levels of A β 42 increase early in the development of dementia,² and studies of A β peptides in CSF have consistently shown that low levels of A β 42 and high concentrations of tau protein are associated with AD and predict incipient AD.^{3–5} Reduced CSF A β 42 is also associated with high brain amyloid load as imaged with Pittsburgh Compound B.⁵

Results from studies examining the relation of plasma concentrations of A β 42 and A β 40 to risk of AD have been less consistent, and the usefulness of plasma A β as a risk biomarker remains controversial.^{6–8} Several studies have reported that either elevated or decreasing plasma A β 42 or A β 42/A β 40 ratio levels in older adults without dementia are associated with increased risk for mild cognitive impairment (MCI), cognitive decline, and AD,^{6,7,9–14} but others have not found this relationship.^{15,16} Still others have found that risk of AD is associated with low

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plasma levels of A β 42, A β 40, or the A β 42/A β 40 ratio.^{8,17–19} Although differences in A β assays, in study design and in populations examined are likely to influence findings, these inconsistencies may also be related to the timing of A β measures in relation to the development of AD, given the dynamic rather than static nature of the underlying neuropathology.²⁰

Individuals with Down syndrome (DS) have increased levels of A β 40 and A β 42 peptides in plasma together with increased risk for AD neuropathology and clinical dementia.^{21–25} The nearly universal presence of AD neuropathology as well as the increased levels of A β peptides have been attributed, at least in part, to the triplication and overexpression of the gene for APP, located on chromosome 21,²⁶ but large individual differences in plasma A β levels and the wide range of age at onset of AD within this population suggest a more complex underlying mechanism. In previous studies of this population, we found that high initial levels of plasma A β 42, but not A β 40, predicted onset of dementia over a 4-year follow-up period.¹¹ The aim of the present study was to expand our previous work by examining the relation of change in levels of A β 40, A β 42, and the A β 42/A β 40 ratio to onset of dementia with longitudinal follow-up and repeated measures of A β peptides.

METHODS Study population. The sample included 225 members of a community-based sample of adults with confirmed DS, without dementia at their initial examination and with multiple measurements of A β peptides. Of these, 191 were among the 207 adults with DS in our previous examination of the relation of initial levels of A β peptides to dementia risk and 37 were

new to the cohort¹¹ (figure 1). All individuals were 40 years of age or older (range 40–78) and resided in New York, Connecticut, New Jersey, or eastern Pennsylvania. Participants were recruited with the help of state and voluntary service provider agencies and were eligible for inclusion in the present study if 1) a family member or correspondent provided informed consent, 2) he or she either provided consent or signed a form acknowledging their assent and willingness to participate, and 3) he or she was willing and able to provide blood samples and had been evaluated at least twice.

Standard protocol approvals, registrations, and patient consents. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of the New York State Institute for Basic Research in Developmental Disabilities, Columbia University Medical Center, and The Johns Hopkins University School of Medicine.

Clinical assessment. Assessments included evaluations of cognition, functional and vocational abilities, behavioral/psychiatric conditions, and health status. Assessments were repeated at 14- to 20-month intervals. Cognitive function was evaluated with a test battery designed for use with individuals varying widely in their premorbid levels of intellectual functioning, as previously described.²⁷ Structured interviews were conducted with caregivers to collect information on adaptive behavior and medical history. Past and current medical records were reviewed for all participants. Participants showing cognitive and functional declines indicative of dementia were evaluated by the study neurologist.

Classification of dementia. To determine the occurrence of dementia and dementia subtypes in participants, data from all available sources were reviewed during a consensus conference. Following recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability,²⁸ participants were classified into 2 groups: 1) dementia, if there was a history of progressive memory loss, disorientation, and functional decline over a period of at least 1 year and if there were no other medical or psychiatric conditions that might result in or mimic dementia present (e.g., untreated hypothyroidism, stroke) ($n = 64$); and 2) without dementia, if they were without cognitive or functional decline or if they exhibited less substantial cognitive and functional declines that did not meet criteria for dementia ($n = 164$). All participants classified as having dementia showed strong and consistent declines in cognition and function over the course of follow-up.

AD was the predominant form of dementia, accounting for 95% of the cases. Participants with evidence of dementia with stroke during the neurologic evaluations or from clinical histories were excluded ($n = 3$), leaving 61 participants with AD for analysis (figure 1). Age at meeting consensus conference criteria for dementia was used to estimate age at onset of AD, recognizing that it is difficult to document the onset of initial symptoms in this population with precision.

Plasma A β 42 and A β 40. Participants were asked to provide a 10-mL venous nonfasting blood sample (K₃ EDTA lavender-top tube) at each assessment cycle, although it was not always possible to obtain a blood sample at every cycle. Plasma levels of A β 42 and A β 40 were measured blind to dementia status using a combination of monoclonal antibody 6E10 (specific to an epitope present on 1–16 amino acid residues of A β) and rabbit antisera R165 (vs A β 42) and R162 (vs A β 40) in a double antibody sandwich ELISA as described previously.^{7,22} The detection

Figure 1 Description of sample

limit for these assays was 5 pg/mL for A β 40 and 10 pg/mL for A β 42. A β 40 and A β 42 levels from each sample were measured twice using separate aliquots. Reliability between measurements was substantial for both peptides ($r = 0.93$ and $r = 0.97$ for A β 40 and A β 42, $p < 0.001$), and we used the mean of the 2 measurements in statistical analyses.

APOE genotypes. APOE genotyping employed standard PCR–restriction fragment length polymorphism methods using *HhaI* (*Cf*01) digestion of an APOE genomic PCR product spanning the polymorphic (cys/arg) sites at codons 112 and 158. Acrylamide gel electrophoresis was used to assess and document the restriction fragment sizes.²⁹ Participants were classified according to the presence or absence of an APOE ϵ 4 allele.

Covariates. Level of intellectual disability was classified into 2 groups based on IQ scores obtained before onset of dementia: mild/moderate (IQ 35–70) and severe/profound (IQ <35). Ethnicity was coded as white or other. We examined statin use, body mass index, and obesity as potential confounders but found that they were not related to A β levels nor to risk of AD and they were therefore not considered further in analyses.

Statistical analyses. In preliminary analyses, we used χ^2 tests for categorical variables and Student t tests and analyses of variance to compare demographic characteristics and A β peptide levels by dementia status. For inferential analyses, we examined the relation of change in A β peptides to risk of dementia. Among participants who developed AD over the follow-up period, change was calculated as the difference between the sample associated with the assessment interval at which AD was first diagnosed (incidence visit) and the baseline visit. For participants who remained without dementia throughout the

follow-up period, change was calculated as the difference between A β peptide levels at the last follow-up and the initial measurement. In preliminary analyses, we examined change in A β as a continuous variable and found an inverse relation between change in A β 42 and risk for AD ($\beta = -0.032$, $p = 0.012$), an inverse relation between change in the A β 42/A β 40 ratio ($\beta = -1.6$, $p = 0.03$), but no relation between change in A β 40 and risk for AD ($\beta = 0.001$, $p = 0.549$). We then categorized change in A β by change groups to detect potential nonlinear threshold effects. We classified A β peptide change into 3 groups based on 0.5 standard deviations of change: 1) no change (no change ± 0.5 SD change); 2) increasing (>0.5 SD change); and 3) decreasing (<0.5 SD change). We used Cox proportional hazards models to estimate the cumulative incidence of dementia and hazard ratio (HR) of dementia by change in A β peptide group, with increasing levels (>0.5 SD change) as the reference group. The time to event variable was time from initial A β peptide measurement to onset of dementia for incident cases and time from the initial A β peptide measurement to last assessment for those who remained without dementia. Because levels of A β 42 and A β 40 were correlated, we used models containing measures of both peptides in all analyses to determine if independent relationships with dementia status were present. All models were adjusted for sex, ethnicity, level of intellectual disability, and the presence of the APOE ϵ 4 allele. (These analyses were repeated using change criteria of 0.25 SD and 0.75 SD. Findings were consistent in all 3 sets of analyses, and only the 0.5 SD results are presented here.)

RESULTS Relation of A β peptides to demographic characteristics. Table 1 presents demographic characteristics and A β peptide levels by dementia status. The mean length of follow-up was 4.1 (± 1.9) years. Over the course of follow-up, 61 participants (27.1%) developed dementia. The mean time from baseline to onset of dementia in cases was 2.8 (± 1.6) years. Levels of A β 40, but not A β 42, increased modestly with age ($r = 0.13$, $p = 0.07$). Participants who subsequently developed dementia were older at baseline than those who remained without dementia throughout the follow-up period (53.7 vs 50.3 years, $p = 0.001$), but did not differ by sex, ethnicity, or level of intellectual disability. The frequency of the APOE ϵ 4 allele was greater in those who developed dementia (26.2% vs 18.3%), but this difference failed to reach significance (table 1).

Relation of change in A β peptide levels to incidence of AD. Increases in plasma A β 40 peptides, decreases in A β 42 peptides, and decreases in the A β 42/A β 40 ratio were significantly related to conversion to dementia over the follow-up period (table 2). Compared with those with increasing plasma A β 40 levels, those with decreasing levels were 60% less likely to develop dementia over the follow-up period (HR = 0.4, 95% CI 0.2–0.9) (table 2). Compared with those with increasing levels of plasma A β 42, those with no change in A β 42 levels were 2.5 times as likely to develop AD (HR = 2.6, 95% CI 1.3–5.2), while those with decreasing levels of plasma A β 42 were 5

Table 1 Demographic characteristics

Characteristics	No dementia	Incident dementia
No.	164	61
Age at baseline, y, mean $\pm$ SD ^a	50.3 $\pm$ 5.2	53.7 $\pm$ 5.4
Sex, n (% women)	109 (66.5)	43 (70.5)
Ethnicity, n (%)		
White	150 (91.5)	56 (91.8)
Nonwhite	14 (8.5)	5 (8.2)
Level of intellectual disability, n (%)		
Mild/moderate	88 (53.7)	34 (55.7)
Severe/profound	76 (43.6)	27 (44.3)
APOE ϵ 4 allele, n (%)	30 (18.3)	16 (26.2)
A β 40, baseline, mean ($\pm$ SEM)	151.9 (4.1)	160.7 (6.8)
A β 40, last follow-up, mean ($\pm$ SEM) ^b	150.1 (4.2)	172.1 (6.7)
A β 40, change, mean ($\pm$ SEM)	−1.9 (4.9)	11.4 (8.3)
A β 42, baseline, mean ($\pm$ SEM)	26.2 (0.86)	25.4 (0.95)
A β 42, last follow-up, mean ($\pm$ SEM) ^a	33.4 (1.1)	25.8 (1.7)
A β 42, change, mean ($\pm$ SEM) ^b	7.2 (1.2)	0.4 (1.6)
A β 42/A β 40, baseline, mean ($\pm$ SEM)	0.20 (0.01)	0.18 (0.02)
A β 42/A β 40, last follow-up, mean ($\pm$ SEM) ^a	0.25 (0.01)	0.16 (0.01)
A β 42/A β 40, change, mean ($\pm$ SEM) ^c	0.05 (0.02)	−0.02 (0.02)

^a $p < 0.001$.

^b $p < 0.01$.

^c $p < 0.05$.

Table 2 Relation of change in A β peptide levels to incidence of Alzheimer disease

Change in A β levels	No. at risk	Dementia, n (%)	Hazard ratio model ^a
Change in A β 40 by group			
Increasing	55	20 (36.4)	1.0 (reference)
No change	112	32 (28.6)	0.8 (0.5–1.5)
Decreasing ^b	58	9 (15.59)	0.4 (0.2–0.9)
Change in A β 42 by group			
Increasing	82	11 (13.4)	1.0 (reference)
No change ^c	115	38 (33.0)	2.6 (1.3–5.2)
Decreasing ^c	28	12 (42.9)	4.9 (2.1–11.4)
Change in A β 42/A β 40 ratio by group			
Increasing	71	8 (11.3)	1.0 (reference)
No change ^c	132	45 (34.1)	3.9 (1.8–8.4)
Decreasing ^c	22	8 (36.4)	4.9 (1.8–13.2)

^a Cox proportional hazard model: hazard ratio (95% confidence interval), adjusted for sex, level of intellectual disability, ethnicity, and presence of the APOE ϵ 4 allele.

^b $p < 0.05$.

^c $p < 0.01$.

times as likely to develop AD (HR = 4.9, 95% CI 2.1–11.4) (table 2) (figure 2). No change and decrease in the ratio of A β 42/A β 40 were also strongly related to the development of dementia. Compared with those with an increasing A β 42/A β 40 ratio over the follow-up period, those whose A β 42/A β 40 ratio did not change and those with a decreasing A β 42/A β 40 ratio were 4 to 5 times as likely to have developed AD (HR = 3.9, 95% CI 1.8–8.4 for those in the no change group; HR = 4.9, 95% CI 1.8–13.2 for those in the decreasing group) (table 2).

Figure 2 Cumulative incidence of dementia by A β 42 change group

AD = Alzheimer disease.

DISCUSSION In a previous study, we found that adults with DS with high initial levels of plasma A β 42, but not A β 40 or the ratio of A β 42/A β 40, had a 2.5-fold increased risk of incident dementia.¹¹ The current study extends this analysis in the same study group to show that declining levels of A β 42 and of the A β 42/A β 40 ratio are also associated with increased risk of incident dementia. Among adults with DS, the association of elevated A β 42 with increased risk of dementia is consistent with studies showing elevated plasma levels of A β 42 in other high-risk populations. Studies of families with AD mutations have shown elevated plasma A β 42 levels in both symptomatic and nonsymptomatic individuals.^{30,31} Plasma A β 42 and A β 42/A β 40 ratio levels were elevated in unaffected familial AD mutation carriers compared with unaffected individuals with familial AD without mutations. However, A β 42 levels were lower in mutation carriers with incipient AD characterized as having a Clinical Dementia Rating = 0.5, supporting the hypothesis that A β 42 decreases prior to overt disease.³⁰ First-degree relatives of patients with late-onset AD without known mutations or genetic variants have also been found to have increased plasma A β 42.³² Among elderly individuals without dementia, plasma levels of A β 42 were also increased in women with MCI, who are at high risk of progression to AD,⁹ and high baseline levels and greater reductions in plasma levels of A β 42 during follow-up have been associated with greater cognitive decline.¹⁰ In contrast, a prospective study examining plasma A β 42 showed no difference in patients with MCI who progressed to AD.¹⁶ Other studies have found that low plasma A β 42 or a low ratio of plasma A β 42/A β 40 was associated with more rapid cognitive decline or with the presence of frank disease.^{17,18,33}

These inconsistencies may be related, at least in part, to the timing of A β measures in relation to disease onset and progression. If conversion to AD is associated with a decline in plasma A β 42 or in the A β 42/A β 40 ratio, then plasma A β levels may already be low in those with MCI or incipient AD. Thus, given the long preclinical period for AD, it is important to control for stage of disease, and this can best be done in prospective, longitudinal studies with repeated peptide measurements in elders who are free of cognitive impairment at their initial assessment. In the current study, the development of dementia in adults with DS who were without dementia at baseline was strongly related to decreases in plasma A β 42, decreases in the A β 42/A β 40 ratio, and increases in plasma A β 40, suggesting that change may be a more sensitive biomarker of risk than level. Compared with individuals with increasing levels of A β peptides, incident dementia was 2.5 to 5 times

more likely among those whose plasma levels of A β 42 or the A β 42/A β 40 ratio did not change or declined by more than 0.5 standard deviations. These findings parallel those from a multiethnic cohort from Northern Manhattan.¹² In that study, decline in plasma A β 42 levels and in the A β 42/A β 40 ratio over a 4.5-year period was associated with a 3-fold increase in the likelihood of AD. In another study, higher initial plasma A β 42 levels and greater reductions in A β 42 levels were associated with more rapid cognitive decline in healthy elders without dementia.¹⁰ Similarly, an increase in the plasma A β 40/A β 42 ratio (comparable to a decreased A β 42/A β 40 ratio) measured at midlife predicted greater decline in a global measure of cognition and in cognitive status as measured by the Telephone Interview for Cognitive Status.¹⁴ These findings suggest that decline in plasma A β 42 or the A β 42/A β 40 ratio might serve as a sensitive biomarker for incipient AD and may reflect aggregation of A β 42 in senile plaques.^{7,12} Our results are also consistent with findings from longitudinal assessments of A β peptides in CSF, where decreases in A β 42 are correlated with cognitive decline in episodic memory and cognitive speed.³⁴ Prior studies, however, have not found significant correlations between levels of CSF and matched plasma samples of A β 42 and A β 40,^{35,36} suggesting that A β levels in CSF and plasma are not related in a simple way and that the source of A β synthesis in these 2 compartments is different.³⁶ It has been suggested that some A β in brain parenchyma is eliminated through the vascular spaces, contributing to A β levels in blood,³⁷ but other studies suggest that platelets are a major source of A β in plasma unrelated to CNS processes.³⁸ Thus, there is as yet no consensus regarding how plasma A β is related to progressive CNS amyloid pathology. In most previous studies, the relationship between CSF and plasma A β levels was examined in cross-sectional samples and compared patients with MCI or established AD with controls without dementia.^{35,36} Future longitudinal studies comparing sequential measures of matched plasma and CSF A β levels may be an effective approach to address this issue.

In the current study, increasing levels of plasma A β 40 were associated with increased risk of AD. In cross-sectional studies, increased levels of A β 40, along with increased levels of A β 42, have been found in plasma of adults with DS.^{21–24} We are not sure what role increasing A β 40 may play in the pathogenesis of AD in DS. We speculate that increasing levels among adults with DS without dementia, who already have very high levels of A β 40, may be a marker of rate of aging.

These new findings add to previous evidence indicating that change in levels of A β peptide in both

blood and CSF are sensitive to progression of neuropathology in AD, both in the general population and among adults with DS. Our study is limited by a relatively small sample size with small numbers in high-risk groups. In addition, individual differences in A β peptide levels, as well as changes in these levels, are imperfectly related to risk of dementia, and the determinants of individual differences in both initial levels and the trajectory of change in A β need to be explored further before these assays can be used to inform diagnosis or predict individual risk. Differences in the formation of oligomeric forms of A β , in levels of autoantibodies to A β , or in other protective factors may modify the effect risk biomarkers. Thus, plasma A β levels are not useful for predicting future onset or to confirm diagnoses for specific individuals with DS at the present time.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Schupf, Dr. Zigman, and Dr. Tang.

DISCLOSURE

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