Serum Aβ Levels as Predictors of Conversion to Mild Cognitive Impairment/Alzheimer Disease in an ADAPT Subcohort

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Recent evidence suggests an association of β-amyloid (Aβ) with vascular risk factors and the medications to treat them, which could potentially obfuscate the usefulness of Aβ for prediction of mild cognitive impairment (MCI) or Alzheimer disease (AD). In a subcohort from the Alzheimer's Disease Anti-inflammatory Prevention Trial (enriched for family history of AD), we investigated whether systolic blood pressure, total cholesterol, triglycerides, serum creatinine, apolipoprotein E, and use of statins and antihypertensives influenced the predictive value of serum Aβ for MCI/AD during a 2-year period. We collected blood samples to quantify serum Aβ from cognitively normal participants (n = 203) at baseline and ascertained the outcome of MCI/AD (n = 24) for a period of approximately 2 years. In an unadjusted model, the lowest quartile of $A\beta_{1-42}$ (hazard ratio (HR) = 2.93, 95% CI (1.02–8.32), P = 0.04) and of the $A\beta_{1-42}/A\beta_{1-40}$ ratio (HR = 3.53, 95% CI (1.24–10.07), P = 0.02), compared with the highest quartile, predicted conversion to MCI/AD, but no impact of $A\beta_{1-40}$ was observed. No relationship between nonsteroidal antiinflammatory drug interventions and Aβ on MCI/AD risk was evident. Once data were adjusted for potential confounders (age, sex, and education), vascular risk factors, and the medications listed above, the lowest quartiles of $A\beta_{1-42}$ (HR = 4.47, 95% CI (1.39–14.39), P = 0.01), and of the $A\beta_{1-42}/A\beta_{1-40}$ ratio (HR 4.87, 95% CI (1.50–15.87), P = 0.01) became strong predictors of conversion to MCI/AD. In this subcohort of individuals at risk for AD, the association of Aβ with vascular risk factors and medications to treat these conditions did not interfere with Aβ's predictive value for MCI/AD.

INTRODUCTION

Sequential processing of the amyloid precursor protein by the β- and γ-secretases results in production of β-amyloid $(A\beta)_{1-40}$ and $A\beta_{1-42}$ fragments. It has been suggested that the imbalance between production and clearance of these peptides leads to their deposition in the brain and subsequent manifestation of the clinical symptoms of Alzheimer disease (AD). Consequently, current therapeutic strategies are aimed at altering Aβ production, aggregation, or clearance, and a number of these are in various stages of preclinical and clinical development (1). However, clinical trials in AD are beset by challenges due to diagnostic variability, uncertainty in early detection, and a lack of availability of biomarkers for therapeutic outcome. As such, evaluation of peripheral Aβ levels for AD diagnosis/prediction and as biomarkers of clinical end points in trials remains an active area of investigation.

Low concentrations of $A\beta_{1-42}$ in cerebrospinal fluid (CSF) have been shown to predict conversion of mild cognitive impairment (MCI) to AD and parallel brain Aβ deposition (2,3). Given the invasive nature of lumbar puncture, its clinical application in MCI and AD diagnosis may be of limited use in routine healthcare settings. Although the origin of blood Aβ remains under investigation, accumulating literature suggests that changes in $A\beta_{1-42}$ or $A\beta_{1-40}$ may be indicative of disease onset and progression and that low $A\beta_{1-42}/A\beta_{1-40}$ ratios are useful in prediction of MCI and/or AD (4–6). Differences among studies in the duration of follow-up prior to conversion have led to differing results pertaining to the predictive value of Aβ toward AD onset and may be attributable to the changes in Aβ levels with preclinical disease progression (6,7). For instance, Schupf and coworkers demonstrated that during a 5-year pe-

riod, high $A\beta_{1-42}$ predicted incipient AD and that 2 years prior to disease onset, a decline in $A\beta_{1-42}$, accompanied by a decline in $A\beta_{1-42}/A\beta_{1-40}$ ratios, predicted conversion to AD (6). Graff-Radford *et al.* demonstrated that during a 4-year period, the $A\beta_{1-42}/A\beta_{1-40}$ ratios in the lower quartiles compared with the highest quartile predicted conversion to MCI/AD (5). Van Oijen *et al.* showed that the $A\beta_{1-42}/A\beta_{1-40}$ ratio in the lowest quartile, driven by high $A\beta_{1-40}$, predicted AD during an average time period of 8 years (4).

Likely reasons for these discrepancies may include population stratification or presence of confounding factors that are associated with AD and also influence $A\beta$ levels. We and others have demonstrated that vascular risk factors of AD (and medications to treat these conditions) are associated with differences in blood $A\beta$ levels (8–14). However, the consequences of such an association on the predictive value of $A\beta$ for MCI/AD is underexplored, having been evaluated in only one longitudinal study thus far, after which the authors reported that $A\beta$ showed little usefulness in AD prediction (10). Therefore, using a longitudinal study design, we investigated whether vascular risk factors and medications to treat these conditions influence the use of blood $A\beta$ to predict conversion to MCI/AD during a 2-year period.

MATERIALS AND METHODS

Study Population and Data Collection

The Alzheimer's Disease Antiinflammatory Prevention Trial (ADAPT) was conducted to test the effects of nonsteroidal antiinflammatory drugs (NSAID) on the prevention of AD. The study participants (n = 2528) were older than 70 years, had a first-degree relative with AD-like dementia, and were considered free of dementia or other cognitive impairment on the basis of results of a neuropsychological test battery performed to assess eligibility for study participation. Tests used for assessment included the Modified Mini-Mental State Examination, the Hopkins Verbal Learning Test—Revised, and the informant-rated Dementia Severity Rating Scale. At the enrollment visit, these individuals were randomly assigned to the study interventions (celecoxib [200 mg twice a day], naproxen sodium [220 mg twice a day], or placebo). The primary outcome measure was development of AD. Full details of data collection, laboratory measurements, and study procedures are available at http://www.jhucct.com/adapt/manall43.pdf and described elsewhere (9).

The Western Institutional Review Board approved this study, and all participants provided written consent. Blood samples were collected at the semiannual visits (baseline for this ancillary study) from 203 cognitively normal participants (ADAPT subpopulation) at the Florida site between 5 and 44 months after the randomization (median 29 months) and 24 subsequently developed MCI (n = 10) or AD (n = 14). While the ADAPT study was ongoing, participants received a standard battery of neuropsychological testing at each annual visit, described elsewhere (15). Once the in-person follow-up ended, as part of this ancillary study the participants were asked to return every 6 months, and they received neuropsychological testing by use of the Repeatable Battery for Assessment of Neuropsychological Status, a reliable and well-validated instrument for the assessment of older adults and other individuals with possible mild-to-moderate dementia. This assessment tool comprises tests of immediate and delayed recall, language, attention, and visual spatial abilities (16,17). Individuals who scored below expectations on either annual or biannual cognitive assessments underwent dementia work-up, which included physical and neurological examinations, laboratory studies (complete blood count, chemistry count, sedimentation rate, vitamin B_{12} and folic acid levels, thyroid test, and syphilis serological test), and neuroimaging (magnetic resonance imaging or computed tomographic scan), as applicable. A more comprehensive neuropsychological assessment was also administered as part of the dementia work-up and consisted of the expanded Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (18). Learning and memory functions were evaluated using the CERAD 10-word, 3-trial list learning task and CERAD delayed recall measure, and Logical Memory I and II of the Wechsler Memory Scale–Revised (19). The CERAD Constructional Praxis test and Judgment of Line Orientation Test measured visuospatial ability (20). Language and/or executive measures included the 15-item Boston Naming Test, Animal Fluency, the Control Oral Word Association Test, and the similarities subtest from the Wechsler Adult Intelligence Test–third Revision (WAIS-III) (21). The Trails A of the Trail Making Test and Digit Symbol from the WAIS-III were used to measure visual scanning and processing speed. Set-shifting (an executive ability) was measured by use of Trails B and the Letter Number Sequencing subtest from the WAIS-III.

AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria and MCI according to Petersen criteria (22,23). The diagnoses represented combined clinical judgment based upon all available data detailed above. All MCI patients were considered to be amnestic MCI, having impairment in memory only. Evidence suggests that amnestic MCI patients may be in a transitional stage between normal aging and AD (24). It has been reported that about 85% of amnestic MCI patients convert to AD during a 7-year period (25). This finding is further supported by results of an imaging study that demonstrated that the pattern of brain atrophy in amnestic MCI patients is typical of that observed in AD patients (26). Thus, because the MCI and AD diagnoses in this sample are on a continuum, it is reasonable to combine them in a single category, thus allowing large enough numbers to supply statistical power.

Sample Collection and Preparation and Aβ Measurements

Serum from blood was prepared and processed using standard laboratory procedures. The serum Aβ content was determined, according to manufacturer's instructions, using enzyme-linked immunoassay kits for human $A\beta_{1-40}$ and $A\beta_{1-42}$, and the interassay and intraassay coefficients of variation were reported to be ≤10% (Invitrogen, Carlsbad, CA, USA). Additional details are provided elsewhere (9).

Apolipoprotein E Genotyping

We extracted DNA from whole blood by using Pure Gene Kits (Gentra Systems, Minneapolis, MN, USA) and performed apolipoprotein E (APOE) genotyping by using previously established methods, as described elsewhere (9).

Statistical Analyses

Baseline differences between cognitively normal participants and those who converted to MCI/AD were compared by using either the Student t test or the χ^2-statistics. The means and standard deviations were used to summarize symmetric continuous variables; and the medians and interquartile ranges were used to summarize nonsymmetric data. The $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio were categorized by their quartiles for subsequent analyses. Cox regression modeling was employed to identify the predictors of the time from baseline to the occurrence of MCI/AD. Model A analyses of Aβ were unadjusted, model B analyses were adjusted for the effect of age, sex, and education, and model C included systolic blood pressure (SBP), serum creatinine, triglycerides, APOE, study interventions, statin and antihypertensive use, and items listed in model B. All analyses were performed using SPSS 13.0 and the significance level was set at 0.05.

RESULTS

Baseline demographic characteristics of the ADAPT sub-population are presented in Table 1. Male sex frequency was higher among individuals with sub-

Table 1. Baseline characteristics of the study population by subsequent diagnostic categories.

Characteristics	Cognitively normal (n = 179)	MCI/AD (n = 24)
	n (%)	
Female	91 (50.8)	7 (29.2)[a]
White	175 (97.8)	24 (100.0)
Statin use	72 (40.2)	9 (37.5)
Antihypertensive use	72 (40.2)	7 (29.2)
APOE ε4+	56 (31.3)	10 (41.7)
Placebo	79 (44.1)	7 (29.2)
Celecoxib	48 (26.8)	7 (29.2)
Naproxen	52 (29.1)	10 (41.7)
	Mean ± SD	
Age, years	76.61 ± 3.9	78.21 ± 3.9
Education, years	14.77 ± 2.8	14.77 ± 3.2
Mini Mental Status Exam score	28.91 ± 1.3	28.50 ± 1.3
Systolic blood pressure, mm Hg	133.02 ± 11.5	135.07 ± 11.7
Serum creatinine, mg/dL[b]	0.94 ± 0.2	0.93 ± 0.2
Total cholesterol, mg/dL[b]	168.50 ± 85.0	162.67 ± 114.5
Triglycerides, mg/dL	194.31 ± 39.9	186.58 ± 35.9
Serum $A\beta_{1-40}$, pg/mL	146.94 ± 55.6	136.22 ± 42.1
	Median (interquartile range)	
Serum $A\beta_{1-42}$, pg/mL	13.06 (6.35–23.46)	6.33 (1.92–21.08)[a]
Serum $A\beta_{1-42}/A\beta_{1-40}$	0.09 (0.04–0.15)	0.05 (0.02–0.13)[a]

[a]P value < 0.05.
[b]Total cholesterol and triglycerides levels were unavailable for 2 individuals who remained cognitively normal.

sequent diagnosis of MCI/AD (Table 1). The median follow-up was 2.08 y (interquartile range 0.92–2.75 years) and did not differ significantly between participants who remained normal and those who converted to MCI/AD. Distribution of individuals who remained cognitively normal and those who converted to MCI/AD is presented in Table 2.

In an unadjusted model, the lowest quartile of $A\beta_{1-42}$ and of the $A\beta_{1-42}/A\beta_{1-40}$ ratio, compared with the highest quartile of each variable, were associated with an increased risk of MCI/AD, though $A\beta_{1-40}$ and MCI/AD risk was unrelated (Table 3, model A). The lowest quartile of $A\beta_{1-42}$ and of the $A\beta_{1-42}/A\beta_{1-40}$ ratio remained significant predictors of MCI/AD after we adjusted for age, education, and sex (Table 3, model B).

Similar to the early findings from the main ADAPT study (27), an increased AD risk in the naproxen arm (hazard

Table 2. Distribution of subjects who converted and those who remained cognitively normal in different quartiles of $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratios.[a]

Aβ quartiles	Cognitively normal (n = 179)	MCI/AD (N = 24)
$A\beta_{1-42}$ quartiles (Q)		
Q1, ≤6 pg/mL	41 (22.9)	12 (50.0)
Q2, 6.1–12 pg/mL	44 (24.6)	5 (20.8)
Q3, 12.1–23 pg/mL	48 (26.8)	2 (8.3)
Q4, >23 pg/mL	46 (25.7)	5 (20.8)
$A\beta_{1-42}/A\beta_{1-40}$ ratios		
Q1, ≤0.04	48 (26.5)	12 (50.0)
Q2, 0.05–0.08	43 (23.8)	6 (25.0)
Q3, 0.09–0.15	47 (26.0)	1 (4.2)
Q4, >0.15	43 (23.8)	5 (20.8)

[a]Data are n (%).

Table 3. Multivariate Cox regression model for prediction of MCI/AD over 2 years (N = 203).

Aβ levels	Hazard rate model A[a]	P value	Hazard rate model B[b]	P value	Hazard rate model C[c]	P value
$A\beta_{1-40}$, pg/mL	1.00 (1.00–1.01)	0.80	1.00 (0.99–1.01)	0.51	1.00 (0.99–1.01)	0.61
$A\beta_{1-42}$ quartiles						
Q1, ≤6 pg/mL	2.93 (1.02–8.32)	0.04	3.43 (1.19–9.85)	0.01	4.47 (1.39–14.39)	0.01
Q2, 6.1–12 pg/mL	1.02 (0.30–3.52)	0.98	1.11 (0.32–3.83)	0.87	0.75 (0.19–2.97)	0.68
Q3, 12.1–23 pg/mL	0.14 (0.05–2.12)	0.30	0.34 (0.63–1.80)	0.18	0.29 (0.05–1.60)	0.15
Q4, >23 pg/mL	1.00		1.00		1.00	
$A\beta_{1-42}/A\beta_{1-40}$ ratios						
Q1, ≤0.04	3.53 (1.24–10.07)	0.02	3.91 (1.36–11.24)	0.01	4.87 (1.50–15.87)	0.01
Q2, 0.05–0.08	1.36 (0.42–4.47)	0.61	1.57 (0.48–5.20)	0.46	1.39 (0.41–4.74)	0.60
Q3, 0.09–0.15	0.32 (0.04–2.77)	0.30	0.21 (0.03–1.93)	0.17	0.23 (0.03–2.14)	0.20
Q4, >0.15	1.00		1.00		1.00	

[a]Model A is unadjusted.
[b]Model B adjusted for age, sex, and education.
[c]Model C adjusted for APOE, SBP, serum creatinine, triglycerides, statin use, NSAID interventions, antihypertensive use and for items in model B. $A\beta_{1-40}$ was adjusted for $A\beta_{1-42}$ quartiles and vice versa. Q4 was used as reference category for both $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratios.

ratio [HR] = 2.19, 95% confidence interval [CI] [0.83–5.76], $P = 0.11$) was detected in this subpopulation, but it was not statistically significant. No influence of NSAID interventions (nor interaction) was observed to be associated with the relationship between $A\beta_{1-42}$ (HR = 3.34, 95% CI [1.10–10.10], $P = 0.03$) and the $A\beta_{1-42}/A\beta_{1-40}$ ratio (HR = 3.77, 95% CI [1.26–11.27], $P = 0.02$) and the risk for conversion to MCI/AD. We next determined the influence of vascular risk factors on the relationship between Aβ and AD. In this subcohort, as expected, statin use was associated with lower total cholesterol levels (t = 4.36, $P < 0.001$); however, statin use was not associated with triglyceride levels (t = –1.15, $P = 0.25$) and therefore only triglycerides were included in these analyses. Adding SBP, triglycerides, APOE, and serum creatinine to model B further strengthened the predictive value of lowest quartile of $A\beta_{1-42}$ (HR = 3.58, 95% CI 1.17–10.10, $P = 0.03$) and the $A\beta_{1-42}/A\beta_{1-40}$ ratio (HR = 4.39, 95% CI 1.38–14.00, $P = 0.01$) on MCI/AD risk. Statin and antihypertensive use is shown to be associated with dementia and AD risk and is also shown to delay functional decline in AD patients, although length of use of these drugs has an impact on this relationship (28–32). We have previously demonstrated that these medications are also associated with Aβ levels in this subcohort (9).

Among the individuals who were using these drugs, approximately 80% users of statin and 60% of users of antihypertensive drugs were also on these treatments at the time of enrollment into ADAPT. The entire period from ADAPT enrollment to MCI/AD diagnosis censor date covers approximately 4 years. Hence, because of a potential for confounding by these medications on the relationship between Aβ and AD, the analyses were further adjusted for these factors, and the lowest quartile of $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio became much stronger predictors of conversion to MCI/AD than in model B (Table 3, model C). In model C for $A\beta_{1-42}$, we also observed a marginal reduction in the risk for MCI/AD with the use of antihypertensive drugs (HR = 0.34, 95% CI 0.11–1.02, $P = 0.05$); however, this effect was not observed for statin use.

DISCUSSION

These findings suggest that blood $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio may be useful in predicting MCI/AD, results that are consistent with two previous longitudinal studies in showing that low $A\beta_{1-42}$ and the ratios predict conversion to MCI/AD and also support the work by Schupf *et al.* showing that low $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratios predict conversion to AD during a 2-year period (5,6). In contrast to the results of van Oijen and

colleagues (4), this and previous studies (5,6) did not show an impact of $A\beta_{1-40}$ on MCI/AD risk.

The most recent publications on NSAID use among cognitively normal individuals indicated benefits as well as an increased risk for AD, and therefore this relationship still requires further investigation (33–35). These findings are from cohort studies, and as such, there is a potential for selection bias or residual confounding by presence of other unmeasured factors. The subcohort in the current study is from a double-blind, placebo-controlled, randomized trial, which is likely to have a better control over bias and confounding than a cohort study. If there is an impact of NSAID use on AD risk, a correlation between Aβ and conversion might be expected if Aβ levels correlate with disease status. In this regard, a lack of association between blood Aβ and NSAID interventions in this subcohort is consistent with the findings from the Vienna Trans-Danube aging study, which showed no direct impact of NSAID on plasma $A\beta_{1-42}$ among community-based elderly individuals (8). Although NSAID interventions did not impact the predictability of $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio on MCI/AD risk, this finding does not preclude possible long-term influences of NSAIDs, which have recently been suggested to reduce AD incidence in the total ADAPT cohort (36).

Previously, Lopez *et al.* evaluated the influence of vascular risk factors, as measured by the presence of infarct detected by magnetic resonance imaging, cystatin C, and APOE, and found Aβ peptides to be weak predictors of AD (10). The parameters of vascular risk factors in the study by Lopez *et al.* are different from those evaluated in the current study, which instead controlled for SBP, triglycerides, creatinine, and APOE and revealed that $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio are excellent predictors of AD. In contrast to the study by Lopez *et al.* (10), in our study we adjusted analyses for statin and antihypertensive use, both of which are associated with AD prevention (28,29) and with Aβ levels (9). This adjustment further increased the predictive value of $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio on conversion to MCI/AD. Given that Lopez and co-workers used a cohort who were at risk for cardiovascular disease, a possibility remains for residual confounding by other vascular factors, such as those investigated in the current study. Other explanations may include population differences; because the ADAPT subcohort was enriched for family history of AD, this cohort was therefore inherently different from the cohort in the study by Lopez *et al.*

This study provides evidence that $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio were sensitive predictors of conversion to MCI/AD during a 2-year period in a population at risk for AD. A longer follow-up of this subcohort will address whether adjustment of vascular risk factors and medications continues to be helpful for assessment of the long-term predictability of blood Aβ levels and risk of MCI/AD and whether NSAID intervention impacts these relationships.

ACKNOWLEDGMENTS

DISCLOSURE

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