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ORIGINAL RESEARCH

Higher Plasma APOC-III Was Associated with a Slower Reduction of β-Amyloid Levels in Cerebrospinal Fluid Among Older Individuals Without Dementia

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Purpose: Although emerging evidence has suggested that apolipoprotein C-III (APOC-III) is involved in the pathogenesis of Alzheimer's disease (AD), the association of APOC-III with longitudinal changes in cerebrospinal fluid (CSF) AD pathologies (β-amyloid (Aβ42) and tau proteins) is not clear. In the present study, we aimed to examine whether plasma APOC-III levels are associated with longitudinal changes in CSF Aβ42, total-tau (t-tau), and phosphorylated-tau (p-tau) levels among older individuals without dementia.

Patients and Methods: Linear mixed models were fitted with plasma APOC-III used as a predictor for longitudinal changes in CSF AD biomarkers over a 7-year period. Data were obtained from the Alzheimer's Disease Neuroimaging Initiative database, and 195 older individuals without dementia (47 subjects with normal cognition (NC) and 148 subjects with mild cognitive impairment (MCI)) with baseline plasma APOC-III measurements were included.

Results: Among older individuals without dementia, we found that the tertiles of plasma APOC-III were associated with changes in CSF Aβ42, but not t-tau or p-tau. Specifically, the CSF Aβ42 reduction for individuals in the highest plasma APOC-III tertile was significantly slower compared with those in the middle tertile, whereas no other pairwise difference was found to be statistically significant.

Conclusion: Among older individuals without dementia, higher plasma APOC-III levels were associated with slower declines in CSF Aβ42.

Keywords: Alzheimer's disease, apolipoprotein C-III, beta-amyloid, tau proteins, longitudinal study

Introduction

Emerging evidence has suggested that apolipoprotein C-III (APOC-III) is involved in the pathogenesis of Alzheimer's disease (AD).[1–9] For example, plasma APOC-III levels were found to be significantly reduced in patients with AD.[6] In cross-sectional studies, higher APOC-III levels in plasma were correlated with better cognitive performance.[3,6] Additionally, a recent longitudinal study found that higher APOC-III levels in CSF were associated with a slower cognitive decline in individuals with mild cognitive impairment (MCI),[1] further supporting that APOC-III may be neuroprotective. A previous study suggested that this beneficial effect of APOC-III on cognition may be because APOC-III is an Aβ-binding

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protein that can promote Aβ efflux and indirectly reduce the accumulation of Aβ in brain.[6] However, to our knowledge, no studies have attempted to examine the longitudinal associations of APOC-III levels in plasma with changes in CSF AD pathologies (including Aβ42, total tau (t-tau) and phosphorylated tau (p-tau)) in older individuals without dementia.

In the cross-sectional analysis, baseline plasma APOC-III levels were analyzed in relation to baseline CSF Aβ42, t-tau and p-tau levels in older individuals without dementia. Further, the longitudinal analysis was conducted with baseline plasma APOC-III used as a predictor for changes in CSF Aβ42, t-tau and p-tau levels over a 7-year period.

Patients and Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI)

This longitudinal study used data extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu; 3 October 2018). The ADNI study was initiated in 2003 with the primary goal of examining whether a variety of markers, such as neuropsychological assessments, serial MRI, PET, and other fluid biomarkers, could be combined to predict the progression of MCI and early AD. Each participant of the ADNI study provided written informed consent, and each ADNI site obtained local institutional review board approval.

Participants

Patients inclusion criteria have been previously described elsewhere,[10] and can be found at the ADNI website (adni.loni.usc.edu). In brief, participants with NC had a Mini-Mental State Examination (MMSE)[11] score ≥24, and a Clinical Dementia Rating (CDR)[12] score of 0. Participants with MCI had an MMSE ≥ 24, a CDR of 0.5, objective memory deficits as measured by delayed recall scores of the Wechsler Memory Scale Logical memory II, preserved activities of daily living, and an absence of dementia.

In this longitudinal study, we included subjects who met criteria for NC and MCI and had baseline plasma APOC-III samples and follow-up quantifications of CSF Aβ42, t-tau, and p-tau levels. At baseline, there was a total of 195 non-demented older individuals, including 47 participants with NC and 148 participants with MC. As shown in Table 1, annual levels of CSF Aβ42, t-tau, and p-tau were examined for up to 7 years.

Determination of APOC-III in Plasma

Plasma APOC-III levels were measured using xMAP multiplex panel (MyriadRBM),[7] details of which can be found at the ADNI website (http://adni.loni.ucla.edu/). The file "Biomarkers Consortium ADNI plasma QC Multiplex data" was downloaded from the ADNI website (3 October 2018). To better approximate a normal distribution, the APOC-III analyte was natural log transformed. Study subjects were divided into tertile groups according to APOC-III levels. Plasma levels of APOC-III were [1.79, 2.09], [2.09, 2.22], and [2.22, 2.61] μg/mL in the lowest, middle and highest tertiles, respectively.

Determination of CSF Aβ42, t-tau, and p-tau

CSF levels of Aβ42, t-tau, and p-tau were determined with the multiplex xMAP Luminex platform,[13] details of which can be found at the ADNI website (adni.loni.usc.edu). The file "UPENNBIOMK_MASTER" was extracted from the ADNI dataset in October 2018. In the present study, yearly CSF Aβ42, t-tau, and p-tau levels were examined for up to 7 years (Table 1).

Table 1 Demographic and Clinical Data by Tertiles of Plasma APOC-III Levels

Clinical Variables	Low (n = 65)	Middle (n = 65)	High (n = 65)	P value
Age, y	75.2 ± 6.63	75 ± 6.65	74.7 ± 7.49	0.9
Education, y	16.3 ± 2.92	16.1 ± 2.82	15.3 ± 2.96	0.1
Female, n (%)	18 (27.7)	23 (35.4)	28 (43.1)	0.186
APOE4, n (%)	26 (40)	26 (40)	31 (47.7)	0.59
MMSE scores	27.4 ± 1.86	27.5 ± 1.55	27.3 ± 2.15	0.97
CSF Aβ42, pg/mL	188 ± 57.2	177 ± 57.2	181 ± 62.2	0.6
CSF t-tau, pg/mL	84.6 ± 42.6	103 ± 57.2	97.5 ± 48.1	0.09
CSF p-tau, pg/mL	31.1 ± 13.8	33.6 ± 16.7	32.9 ± 16	0.8
Plasma APOC-III, μg/mL	2 (0.08)	2.15 (0.04)[a]	2.32 (0.08)[b,c]	<0.001
Follow-Up Visits, n Subjects				
Baseline	65	65	65	
1 y	65	65	65	
2 y	19	24	19	
3 y	16	19	15	
4 y	12	11	18	
5 y	6	7	8	
6 y	2	3	5	
7 y	0	2	0	

Notes: Comparison between tertile 1 and tertile 2 is marked behind "tertile 2", [a]$p < 0.05$. Comparison between tertile 1 and tertile 3 is marked behind "tertile 3", [b]$p < 0.05$. Comparison between tertile 2 and tertile 3 is marked behind "tertile 3", [c]$p < 0.05$.

Abbreviations: MMSE, Mini-Mental State Examination; APOC-III, apolipoprotein C-III; Aβ42, β- amyloid 42; t-tau, total tau; p-tau, phosphorylated tau

Statistical Analyses

First, we applied Kruskal–Wallis tests and x2 tests to assess differences in demographic and clinical variables across the tertiles of APOC-III levels. Second, to examine the cross-sectional relationships between APOC-III and CSF AD biomarkers, Kruskal–Wallis tests were conducted. Third, to evaluate the association of baseline plasma APOC-III with changes in CSF AD biomarkers over time, linear mixed models were fitted for each CSF AD biomarker (CSF Aβ42, t-tau, and p-tau). All these models were adjusted for age, sex, education and APOE4 genotype. Further, each model included a random intercept for each subject. All statistical analyses were conducted using R software (V.3.6.0).

Results

Demographic and Clinical Variables

The demographic and clinical variables of the study participants by tertiles of plasma APOC-III are demonstrated in Table 1. We did not find significant differences in age or educational attainment across tertiles. Characteristics (sex, percentage of subjects with the APOE4 genotype or MMSE[11] scores) did not differ by APOC-III tertiles (Table 1). In addition, we did not find a significant difference in plasma APOC-III levels between males and females (t = −1.68, p = 0.095). The numbers of subjects present at each follow-up visit are also listed in Table 1.

Associations of Plasma APOC-III Levels with CSF AD Pathologies

To examine the cross-sectional associations of tertiles of plasma APOC-III with CSF AD pathologies, Kruskal–Wallis tests were performed. However, no significant association of tertiles of plasma APOC-III with CSF AD pathologies was observed (all p > 0.05; Table 1, Figure 1).

Longitudinal Change Models

First, to evaluate the association of baseline plasma APOC-III levels (categorized as tertiles) with changes in CSF AD biomarkers over time, linear mixed models were fitted. We found that tertiles of plasma APOC-III were associated with changes in CSF Aβ42, but not t-tau or p-tau (Table 2 and Figure 2). In addition, a plot of individual CSF Aβ42 concentrations over time across the tertiles has also been displayed (Figure S1). Specifically, as shown in Table 3 and Figure 2, the CSF Aβ42 reduction for individuals in the highest APOC-III tertile was significantly slower compared with those in the middle (the middle tertile of APOC-III – the highest tertile of APOC-

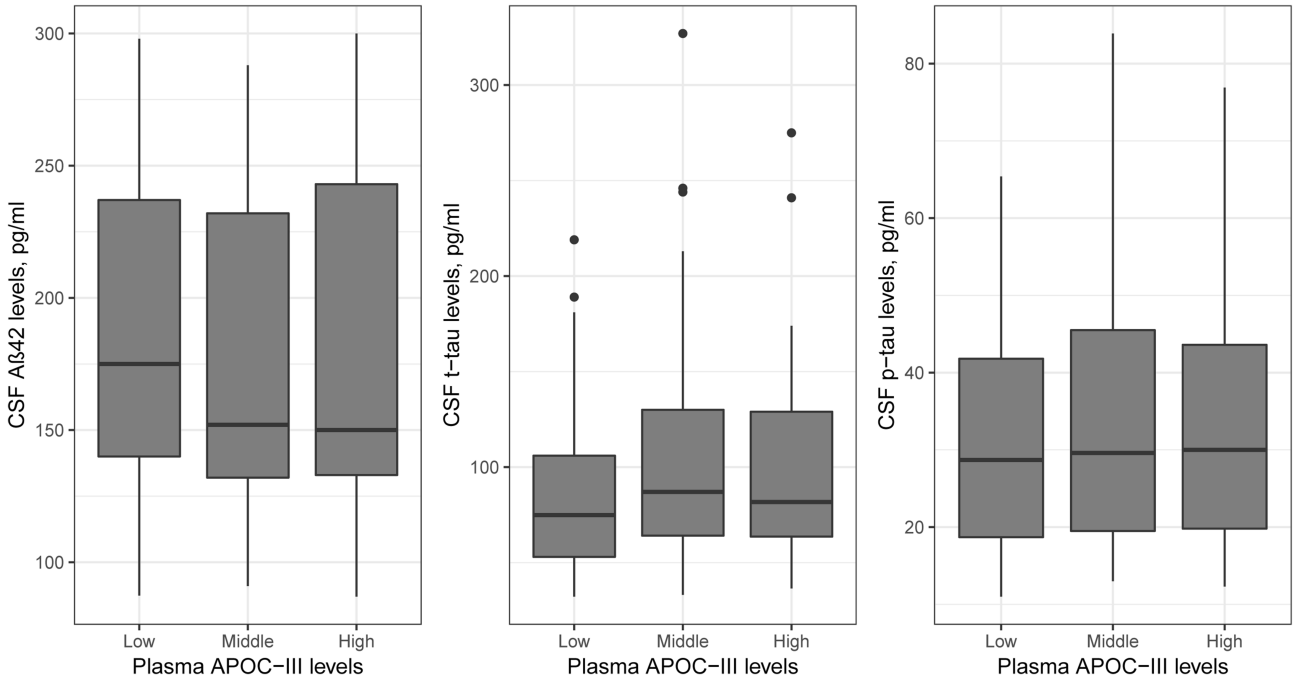

Figure 1 Associations of tertiles of plasma APOC-III with CSF AD biomarkers among older individuals without dementia. No significant associations of tertiles of plasma APOC-III with CSF AD pathologies were observed (all p > 0.05).

Abbreviations: APOC-III, apolipoprotein C-III; Aβ42, β-amyloid 42; t-tau, total tau; p-tau, phosphorylated tau.

Table 2 Summary of Linear Mixed Models Examining the Associations of Plasma APOC-III with Changes in CSF AD Pathologies

Dependent Variable: CSF Aβ42			
Predictors	Estimate	SE	P value
Middle APOC-III × time	−0.2453	0.9750	0.8013
High APOC-III × time	1.9053	0.9568	**0.0464**
Dependent Variable: CSF t-tau			
Predictors	Estimate	SE	P value
Middle APOC-III × time	0.6904	1.2410	0.5780
High APOC-III × time	−0.5342	1.2334	0.6649
Dependent Variable: CSF p-tau			
Predictors	Estimate	SE	P value
Middle APOC-III × time	0.1225	0.8038	0.8788
High APOC-III × time	0.4625	0.7889	0.5577

Note: The bold value indicates a statistically significant difference with a p-value < 0.05. Estimates are unstandardized values, representing the amount of change in each CSF AD biomarker per year. All linear mixed models were adjusted for age, education, sex and APOE4 genotype.

Abbreviation: APOC-III, apolipoprotein C-III; Aβ42, β-amyloid 42; t-tau, total tau; p-tau, phosphorylated tau.

III: estimate = −2.151, SE = 0.909, p = 0.0484), whereas no other pairwise difference was found to be statistically significant (all p > 0.05, Table 3) after correcting for multiple comparisons using Tukey method.

In addition, we examined the association of plasma APOC-III with changes in CSF biomarkers from baseline to 1-year follow-up due to the fact that this approach may seem to have the least "survival" bias (Please see supplementary information: Table S1 and Figure S2).

Discussion

In the present study, we investigated the association of APOC-III levels in plasma with changes in CSF AD biomarkers over time among older individuals without dementia. We found that the tertiles of plasma APOC-III were associated with changes in CSF Aβ42, but not t-tau or p-tau. Specifically, the CSF Aβ42 reduction for individuals in the highest plasma APOC-III tertile was significantly slower compared with those in the middle tertile, whereas no other pairwise difference was found to be statistically significant.

In terms of the biology of APOC-III, it is primarily expressed in the liver and intestine and has an important role in lipid metabolism.[14] An increasing amount of evidence has suggested that APOC-III might also be involved in the pathogenesis of AD. For instance, the APOC-III 3017G allele was found to be associated with decreased risk of AD among individuals without the presence of the APOE4 genotype.[9] In cross-sectional studies, levels of APOC-III in plasma were reduced in patients with AD[6] and were positively correlated with cognitive performance.[3,6] Additionally, one recent prospective and longitudinal study showed that higher CSF APOC-III levels were associated with a slower cognitive decline in individuals with MCI.[1] However, the mechanisms underlying this potentially neuroprotective effect of APOC-III on cognition

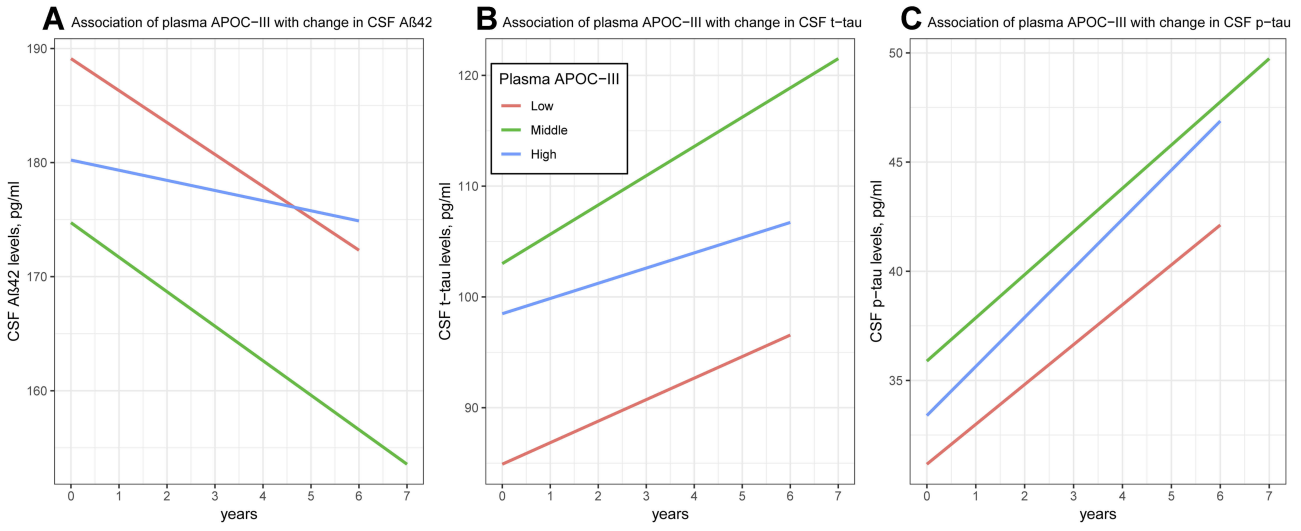

Figure 2 Associations of baseline plasma APOC-III levels with changes in CSF AD pathologies. The tertiles of plasma APOC-III were associated with changes in CSF Aβ42 (**A**), but not t-tau (**B**) or p-tau (**C**). Specifically, the CSF Aβ42 reduction for individuals in the highest APOC-III tertile was significantly slower compared with those in the middle (the middle tertile of APOC-III – the highest tertile of APOC-III: estimate = −2.151, SE = 0.909, p = 0.0484), whereas no other pairwise difference was found to be statistically significant (all p > 0.05).

Abbreviations: APOC-III, apolipoprotein C-III; Aβ42, β-amyloid 42; t-tau, total tau; p-tau, phosphorylated tau.

Table 3 Multiple Comparisons Across the Plasma APOC-III Groups

Contrast	CSF Aβ42 Levels		
	Estimate	SE	P value
Low APOC-III vs Middle APOC-III	0.245	0.979	0.9660
Low APOC-III vs High APOC-III	−1.905	0.961	0.1177
Middle APOC-III vs High APOC-III	−2.151	0.909	**0.0484**

Note: The bold value indicates a statistically significant difference with a p-value <0.05. Tukey method was used for multiple comparison correction. Estimates are unstandardized values, representing the amount of change in CSF Aβ42 per year.
Abbreviation: APOC-III, apolipoprotein C-III; Aβ42, β-amyloid 42.

remain elusive. One approach for examining the mechanism by which APOC-III affects cognitive decline is to investigate the association of APOC-III with longitudinal reductions in CSF Aβ42. In the present study, we provided in vivo evidence that higher CSF APOC-III levels may decelerate reduction in CSF Aβ42 in non-demented older adults, supporting the notion that APOC-III may be a potential agent that can slow disease progression in the early stage of AD. However, the precise mechanism is not clear. Levels of Aβ42 in CSF demonstrated a substantial reduction in patients with AD as reported in previous studies,[15–19] probably resulted from aggregation and accumulation of Aβ42 in brain or a failure of Aβ42 clearance which contributes to decreased amount of Aβ42 proteins transport to CSF.[20] APOC-III, an amyloid-binding protein, may promote Aβ efflux and indirectly reduce the deposition of Aβ in the brain parenchyma.[6] However, further preclinical studies are needed to clarify the precise mechanisms underlying the relationship between APOC-III and amyloid pathology. Taken together, our data supported the notion that APOC-III may be a major pathogenic factor of AD after Aβ and tau.

Several limitations of this longitudinal study should be noted. First, the findings of this study should be interpreted with caution because of a potential selection bias. Further studies, especially population-based studies, should be conducted to replicate our results. In addition, the observational nature of our study limits our ability to differentiate whether increased APOC-III leads to, results from, or is just correlated with changes in amyloid pathology.

In conclusion, among older individuals without dementia, higher plasma APOC-III levels were associated with slower declines in CSF Aβ42. It should be explored in further studies if modification of APOC-III level slows disease progression.

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Disclosure

The author reports no conflict of interest in this work.

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