



Longitudinal Alzheimer’s Blood Biomarkers and Trajectories in a Cognitively Healthy APOE ε4 Cohort

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BACKGROUND

Alzheimer’s Disease (AD) is a neurodegenerative process characterized by deposition of Amyloid-Beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau proteins. People who are carriers of the APOE ε4 allele have been shown to be at an increased risk of memory decline and development of Alzheimer’s Disease (AD).¹ Diagnosis of AD has primarily been based on clinical presentation and neuropsychiatric testing, with the latter having been shown to be quite effective in monitoring for cognitive impairment.^{2,3} Confirmatory testing historically has been confined to either Cerebrospinal Fluid (CSF) biomarker studies or imaging modalities such as Positron Emission Tomography [PET] scans assessing amyloid plaque burden. Recent efforts are focused on evaluating blood based biomarkers as an alternative diagnostic measure.

OBJECTIVES

To compare the variance of different blood based biomarkers longitudinally amongst an APOE ε4 genetically enriched population who are neuropsychologically healthy at enrollment who convert to a diagnosis of AD versus those who do not convert.

METHODS

We performed a prospective longitudinal study of an APOE ε4 genetically enriched population without cognitive impairment at time of enrollment. Neuropsychological testing and functional status were followed every 2 years with blood based Alzheimer’s biomarkers obtained within 2 weeks of study visits, including Amyloid Beta 40 (Aβ40), Amyloid Beta 42 (Aβ42), Amyloid Beta 42/40 ratio (Aβ42/40), phosphorylated tau 217 (p-Tau217), Glial Fibrillary Acidic Protein (GFAP), and the logarithmic transformation of Neurofilament Light (NFL). Determination of transition from normal cognition to Mild Cognitive Impairment (MCI) or AD was based on clinical evaluation, neuropsychological assessments and functional status.

RESULTS

51 individuals with APOE ε4 allele expression were included in this study, with 35 converting from normal cognition to MCI/AD over the course of the study. The mean initial p-tau217 was significantly higher in converters compared to non-converters (0.741 [SD 0.464] and 0.476 [SD 0.307], respectively; p=0.0430); there were no statistically significant differences found among the other initial biomarker values (Table 1). Longitudinal trajectories of the biomarkers showed that only two were shown to have significant linear change during the overall follow-up period, including p-Tau217 (mean slope [95%CI]: 0.076 [0.054, 0.098]; p <0.0001) and GFAP (mean slope [95%CI]: 0.044 [0.013, 0.076]; p=0.0068) (Table 2 and Figure 1). During the late period (after mean conversion age), no significant differences in annual change of biomarkers were seen between converters and non-converters (Figure 2).

TABLE 1: PATIENT AND INITIAL BIOMARKER CHARACTERISTICS, BY CONVERTER STATUS

	Converter (N=35)	Non-Converter (N=16)	Total (N=51)	p value
Outcome - subcategory				-
AD	1 (2.9%)	0 (0.0%)	1 (2.0%)	
MCI-Amnesic	26 (74.3%)	0 (0.0%)	26 (51.0%)	
MCI-Other	8 (22.9%)	0 (0.0%)	8 (15.7%)	
None	0 (0.0%)	16 (100.0%)	16 (31.4%)	
Baseline age; mean (SD)	62.3 (8.6)	67.9 (9.1)	64.1(9.039)	0.0402 ¹
Conversion age; mean (SD)	77.0 (6.4)	-	-	-
Gender				>0.9999
Female	26 (74.3%)	12 (75.0%)	38 (74.5%)	
Male	9 (25.7%)	4 (25.0%)	13 (25.5%)	
Race/ethnicity				0.37592
Hispanic	3 (8.6%)	1 (6.3%)	4 (7.8%)	
Native American	0 (0.0%)	1 (6.3%)	1 (2.0%)	
White	32 (91.4%)	14 (87.5%)	46 (90.2%)	
E4 copies				0.79632
None	13 (37.1%)	5 (31.3%)	18 (35.3%)	
One	14 (40.0%)	8 (50.0%)	22 (43.1%)	
Two	8 (22.9%)	3 (18.8%)	11 (21.6%)	
Any E4				0.76052
Age at initial biomarker; mean (SD)	70.8 (7.1)	74.0 (7.7)	71.8 (7.4)	0.1485 ¹
Initial biomarker level; mean (SD)				
Abeta40	117.442 (34.353)	108.928 (33.379)	114.771 (33.951)	0.4115 ¹
Abeta42	5.731 (1.829)	5.527 (1.787)	5.667 (1.800)	0.7104 ¹
AMYR	0.050 (0.012)	0.051 (0.007)	0.050 (0.011)	0.6887 ¹
p-tau217	0.741 (0.464)	0.476 (0.307)	0.658 (0.436)	0.0430¹
GFAP	212.319 (99.327)	182.977 (85.425)	203.114 (95.326)	0.3126 ¹
log(NF Light)	3.314 (0.601)	3.207 (0.453)	3.280 (0.557)	0.5301 ¹

¹T-test. ²Fisher Exact

TABLE 2: STANDARDIZED LINEAR ANNUAL CHANGE OF BIOMARKERS DURING THE OVERALL FOLLOW-UP PERIOD

Biomarker	Slope (95%CI)	P
AB40	0.019 (-0.009, 0.047)	0.1883
AB42	-0.002 (-0.030, 0.025)	0.8785
AMYR	-0.024 (-0.050, 0.002)	0.0658
p-Tau217	0.076 (0.054, 0.098)	<0.0001
GFAP	0.044 (0.013, 0.076)	0.0068
NFL	0.030 (-0.004, 0.063)	0.0802

Biomarker measures standardized to standard normal (mean=0, standard deviation=1). Slope estimated constructed from linear mixed model adjusting for age at initial biomarker collection.

FIGURE 1: STANDARDIZED LINEAR SLOPE OF BIOMARKERS DURING THE OVERALL FOLLOW-UP PERIOD

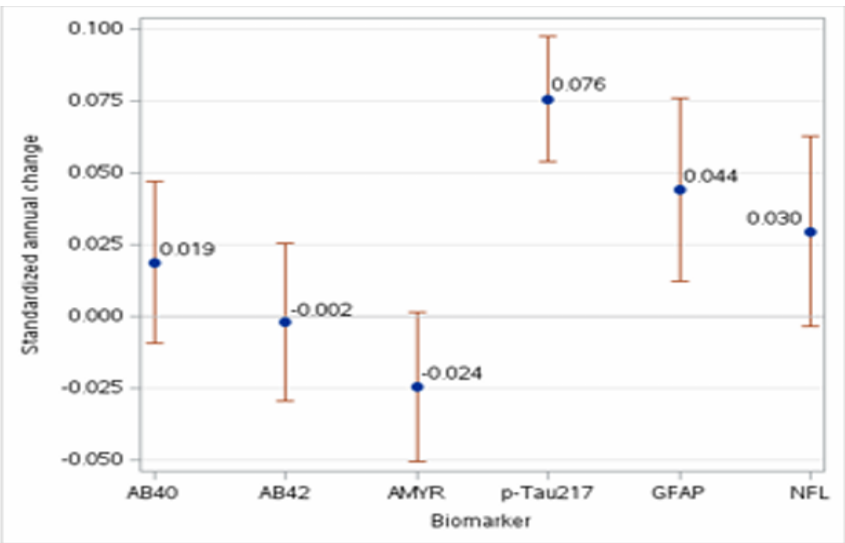
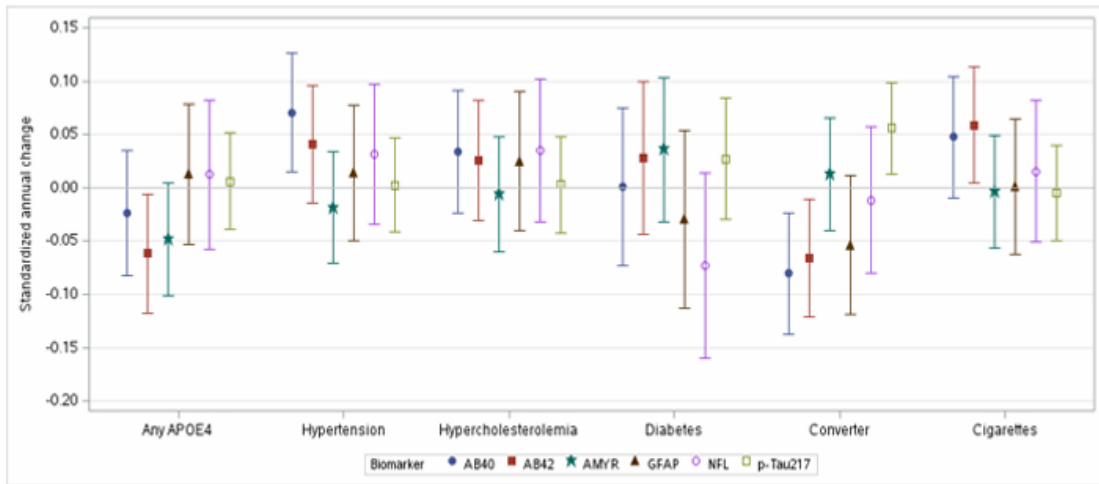


FIGURE 2: DIFFERENCE ON STANDARDIZED LINEAR ANNUAL CHANGE OF BIOMARKERS DURING THE OVERALL FOLLOW-UP PERIOD BETWEEN STUDY GROUPS



DISCUSSION

Plasma p-tau217 showed the greatest divergence both cross sectionally and longitudinally in converters vs non-converters, with converters also having significantly accelerated increases in p-tau217 compared to non-converters. These findings suggest the possible utility of serial p-tau217 testing for monitoring and initiating prompt interventions in individuals who develop cognitive decline. Additionally, our findings highlight the need to consider medical co-morbidities when interpreting biomarker values. Further analyses are warranted in a larger population to evaluate the true power of our findings.

REFERENCES

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