High precision plasma amyloid-β 42/40 predicts current and future brain amyloidosis

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Background

Alzheimer disease (AD) is the most common cause of dementia in older adults. A key neuropathological feature of AD is extracellular amyloid plaques comprised of amyloid β-peptides (Aβ) including lengths of 42 and 40 amino acids (Aβ42 and Aβ40, respectively). Cerebrospinal fluid (CSF) levels of Aβ42, total tau (tTau), and phosphorylated tau181 (pTau) are well established biomarkers of AD brain pathology, but their assessment requires a lumbar puncture. Amyloid PET scans are also well validated, but use radiation, are costly and have limited availability. Prior AD drug trials recruited participants based on a clinical syndrome of AD dementia later found that approximately 25% of study participants did not have detectable brain amyloidosis. More recent AD drug trials have used CSF biomarkers and amyloid PET to confirm that potential participants have brain amyloidosis. A recent prevention trial that screened cognitively normal individuals for brain amyloidosis resulted in a 70% screen failure rate; the time and expense for screening these participants was substantial. A blood-based biomarker would enable more rapid and inexpensive screening of potential participants.

Objective

To evaluate the diagnostic accuracy of plasma Aβ42/Aβ40 for brain amyloidosis, using amyloid PET as a reference standard.

Methods

Using an immunoprecipitation and liquid chromatography-mass spectrometry assay, we measured Aβ42/Aβ40 in plasma and CSF samples from 158 mostly cognitively normal individuals that were collected within eighteen months of an amyloid PET scan. CSF Aβ42, total tau (tTau) and phosphorylated tau 181 (pTau) were measured with Roche Elecsys immunoassays.

Results

Table. 1. Baseline cohort characteristics. The average interval between the plasma collection and the amyloid PET scan was 0.26 ± 0.35 years (mean ± standard deviation). Compared to amyloid PET-negative individuals, individuals who were amyloid PET-positive were older, more likely to carry an *APOE* ε4 allele, more likely to have cognitive impairment, and had lower CSF Aβ42 and higher CSF tTau and pTau.

	Amyloid PET-negative		Amyloid PET-positive		
Characteristic	n=		n=		p=
Age at plasma collection (years)	115	60.8 ± 6.7	43	71.4 ± 6.8	<0.0001
Sex (n, % Female)	115	72, 63%	43	30, 70%	N.S.
Years of education	115	15.9 ± 2.2	43	15.2 ± 3.2	N.S.
APOE ε4 status (n, % carrier)	113	39, 35%	43	27, 63%	0.001
CDR 0/0.5/1/2/3 (% >0)	115	111/4/0/0/0 (3%)	43	37/5/1/0/0 (14%)	0.04
MMSE (out of 30)	115	29.4 ± 0.8	43	29.0 ± 1.6	0.02
IPMS Plasma Aβ42/Aβ40	115	0.128 ± 0.009	43	0.115 ± 0.006	<0.0001
Amyloid PET centiloid	115	1.0 ± 5.5	43	61.5 ± 32.6	<0.0001
AV45 SUVR	27	0.91 ± 0.12	14	2.24 ± 0.64	<0.0001
PIB SUVR	88	1.05 ± 0.10	29	2.26 ± 0.66	<0.0001
IPMS CSF Aβ42/Aβ40	105	0.134 ± 0.016	40	0.077 ± 0.016	<0.0001
Elecsys CSF Aβ42 (pg/ml)	112	1272 ± 531	40	771 ± 297	<0.0001
Elecsys CSF tTau (pg/ml)	112	177 ± 60	40	302 ± 111	<0.0001
Elecsys CSF pTau (pg/ml)	112	15.7 ± 5.6	40	29.7 ± 13.1	<0.0001

Results

Plasma Aβ42/Aβ40 was highly concordant with current amyloid PET status

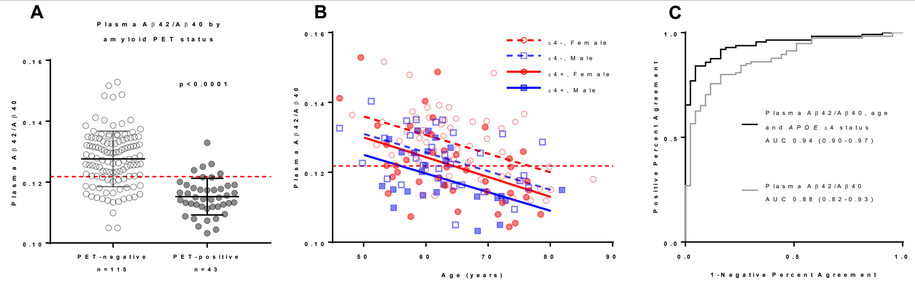


Figure 1. Diagnostic accuracy of plasma Aβ42/Aβ40 for amyloid PET status. A) Plasma Aβ42/Aβ40 was highly concordant with amyloid PET status, with a ROC AUC of 0.88. **B)** Plasma Aβ42/Aβ40 levels varied by age, sex, and *APOE* ε4 status. **C)** After accounting for the effects of age and *APOE* ε4 status, the diagnostic accuracy of improved to 0.94.

Plasma Aβ42/Aβ40 predicted future amyloid PET status

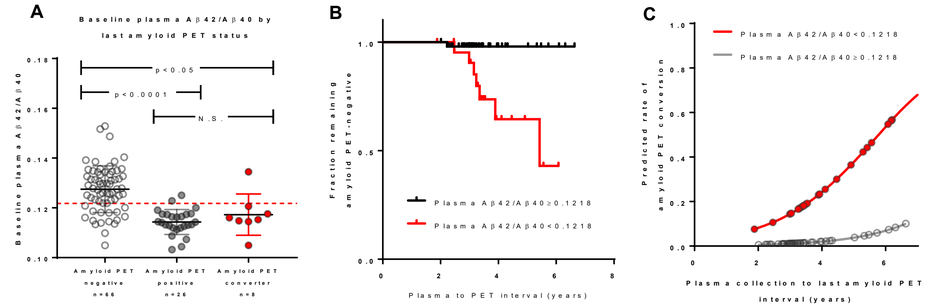
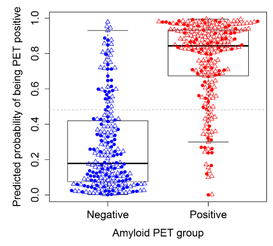


Figure 2. Plasma Aβ42/Aβ40 predicted future amyloid PET status. A) Eight individuals with a negative baseline amyloid PET scan at the time of plasma collection later became amyloid PET positive (average interval 3.9 ± 1.4 years); seven of the eight had a positive plasma Aβ42/Aβ40 at baseline. **B)** Individuals with a positive plasma Aβ42/Aβ40 at baseline were more likely to become amyloid PET positive. **C)** By logistic regression, individuals with a positive plasma Aβ42/Aβ40 at baseline had a 15-fold increased risk of conversion to amyloid PET-positive.

Follow-up studies



Cohort	cutoff	specificity	sensitivity	accuracy	AUC
AIBL	0.506	0.82	0.83	0.88	0.93
BioFinder	0.488	0.84	0.86	0.85	0.90
ADNI	0.479	0.82	0.83	0.82	0.87
Combined	0.482	0.80	0.86	0.83	0.90

Figure 3, Table 2. Plasma Aβ42/Aβ40 combined with *APOE* ε4 status had high concordance with amyloid PET status in other cohorts. ROC AUCs ranged from 0.87-0.93, with a combined value of 0.90. Samples were from Australian Imaging, Biomarkers and Lifestyle study (AIBL, PI Colin Masters), the Swedish Biofinder study (PI Oskar Hansson), and the Alzheimer Disease Neuroimaging Initiative (ADNI, PI Michael Weiner). Combined n=468.

Major Findings

- **Plasma Aβ42/Aβ40, especially when combined with age and *APOE* ε4 status, was highly predictive of current amyloid PET status**
- **Individuals with a positive plasma Aβ42/Aβ40 but negative amyloid PET scan were likely to become amyloid PET positive (15-fold greater risk)**

Discussion

The most immediate use of the plasma Aβ42/Aβ40 assay is screening for brain amyloidosis in potential participants for AD drug trials. Age and *APOE* ε4 status could be used to improve the accuracy of the screen. If the plasma Aβ42/Aβ40 screen were positive, then a confirmatory test such as amyloid PET or CSF biomarkers could be performed, depending on the needs of the study. If the plasma Aβ42/Aβ40 test combined with age and *APOE* ε4 status continues to demonstrate very high accuracy in diagnosis of brain amyloidosis, a single blood test including plasma Aβ42/Aβ40 and *APOE* genotype may be used for study inclusion without a need for confirmatory amyloid PET or CSF. We expect that even after correction for covariates, a small number of individuals will have false positive or false negative results based on plasma Aβ42/Aβ40 caused by variations in pre-analytical conditions, imprecision in the assay, or biological variation. It remains to be determined whether testing with plasma Aβ42/Aβ40 alone versus plasma Aβ42/Aβ40 followed by confirmatory testing with amyloid PET or CSF biomarkers results in clinically significant differences, especially considering the additional burdens and costs associated with the confirmatory tests. An important limitation of this study is that the cohort was designed to evaluate the correspondence of plasma Aβ42/Aβ40 with brain amyloidosis, not symptomatic AD. More comprehensive studies are planned to evaluate the relationship between plasma Aβ42/Aβ40 and symptomatic AD, which will help to assess the clinical utility of this assay. If further validated, this assay will accelerate progress towards an effective therapy for AD by decreasing the time, cost and risk of drug trials, and one day enabling a blood test in the clinic to identify patients who could benefit from disease modifying treatment.

References

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