Comparative performance of plasma Aβ42/Aβ40 and p-tau181 for the detection of early brain amyloid deposition in individuals with subjective cognitive decline

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BACKGROUND

In the last years, **blood-based biomarkers** have shown high accuracy for the identification of early alterations of Alzheimer's disease (AD). Among them, plasma Aβ42/Aβ40 and p-tau181 have been proved to be reliable biomarkers of brain amyloid deposition. However, the quantification of these molecules in plasma, mainly Aβ42, presents analytical difficulties and **high reliability analytical assays** are needed in order to avoid biased conclusions about the comparative performance of both biomarkers. In this study, we aim to avoid these uncertainties by the introduction of a high sensitivity assay based on HPLC-MS for the quantification of Aβ peptides in plasma.

OBJECTIVE

To compare the ability of **plasma Aβ42/Aβ40** ratio measured with a mass spectrometry-based assay and **plasma p-tau181** measured with a high-sensitivity technology to detect **early brain amyloid deposition** in individuals at risk of AD.

METHODS

152 subjects with subjective cognitive decline (SCD) from the FACEHBI cohort were included in the present study, of which 16% were Aβ-PET (+). Plasma Aβ40 and Aβ42 were quantified with a high sensitivity antibody-free mass spectrometry-based assay (ABtest-MS, Araclon Biotech). Plasma p-tau181 was measured with Simoa® pTau-181 V2 Advantage Kit (Quanterix). The ability of plasma biomarkers alone, combined or after the addition of demographic covariates, to detect Aβ-PET positivity was assessed by logistic regression and ROC curve analysis.

RESULTS

1. Characteristics of the study population

Table 1. Characteristics of the study population. Data are median values (interquartile range) or number of cases (%). Differences between Aβ-PET (-) and Aβ-PET (+) groups were tested using Mann-Whitney and Chi-square tests, as appropriate.

	All	Aβ-PET (-)	Aβ-PET (+)	*P* value
Participants	152	125 (82%)	27 (18%)	
Age, years	66.0 (60.0-70.0)	64 (60.0-69.0)	70 (67.0-72.0)	**.001**
Female	95 (63%)	82 (66%)	13 (48%)	.139
***APOE* ε4**				**<.0001**
1 alleles	39 (26%)	23 (18%)	16 (59%)	
2 alleles	3 (2%)	2 (2%)	1 (4%)	
MMSE, score	30 (29-30)	29 (29-30)	30 (29-30)	.361
FBB-PET, CL	-1.43 (-6.66-6.57)	-3.6 (-7.8-1.5)	32.8 (21.2-60.6)	**<.0001**
Aβ42/Aβ40	0.258 (0.236-0.276)	0.261 (0.244-0.278)	0.216 (0.199-0.236)	**<.0001**
p-tau181, pg/ml	1.81 (1.38-2.40)	1.71 (1.32-2.07)	2.67 (2.28-3.19)	**<.0001**

Plasma Aβ42/Aβ40 levels were significantly reduced in the Aβ-PET (+) group compared to Aβ-PET (-) subjects, whereas the opposite was observed for plasma p-tau181 (*P*<.0001 in both cases, Mann-Whitney test) (**Table 1** and **Figure 1**).

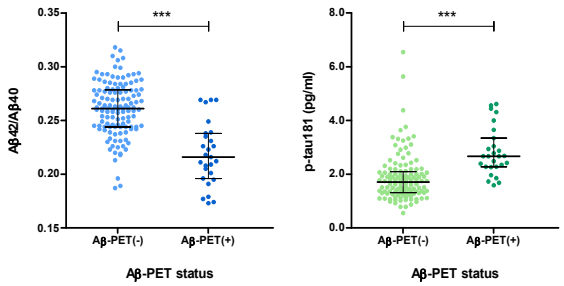

*Figure 1. Box and whiskers plots of plasma Aβ42/Aβ40 and p-tau181 between Aβ-PET groups. *** P < .0001, Mann-Whitney test.*

2. Discriminative ability of Aβ-PET status

Plasma Aβ42/Aβ40 ratio and p-tau181 identified Aβ-PET status with an AUC of 0.86 (95% CI 0.78–0.94) and 0.83 (95% CI 0.76–0.90), respectively (**Figure 2**). At the maximum Youden index, both plasma biomarkers presented a sensitivity of 81.5%, whereas Aβ42/Aβ40 ratio presented slightly superior specificity (84.0%) and overall accuracy (83.6%) than p-tau181 (80.8% and 80.9%, respectively) (**Table 2**).

The combination of plasma biomarkers yielded an AUC of 0.88 (95% CI 0.82-0.95). The inclusion of demographic covariates (age and APOE ε4 number of alleles) increased the AUC up to 0.90 (95% CI 0.85-0.96) (full model). Both Aβ42/Aβ40 and p-tau181 contributed significantly to this model (*P*<.0001 and *P*=.04, respectively). The full model significantly outperformed p-tau181 alone (ΔAUC=0.07, *P*=.04), but did not differ from Aβ42/Aβ40 (ΔAUC=0.04, *P*=.09) (**Table 2**).

Goodness of fit was assessed using AIC. Plasma Aβ42/Aβ40 model presented lower AIC (101.3) than the model composed of plasma p-tau181 (AIC=115.7).

The combination of both biomarkers yielded AIC=94.7, and the inclusion of demographic covariates did not further improve the fit in this case (AIC=94.4).

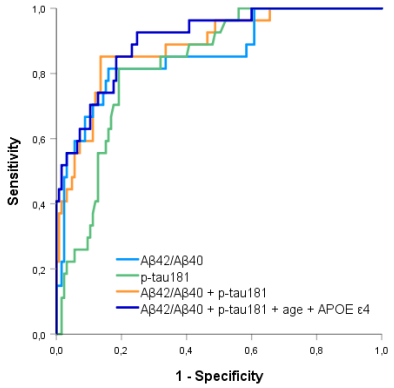

Figure 2. ROC curves for discriminating Aβ-PET status.

*Table 2. Performance of predictive models to identify Aβ-PET status. * P values correspond to the comparison of AUC versus the full model using DeLong test.*

Biomarker 1	Biomarker 2	Covariates	AUC (95% CI)	*P* value*	Sen (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)
Aβ42/Aβ40	-	-	0.86 (0.78-0.94)	ns	81.5	84.0	52.4	95.5	83.6
p-tau181	-	-	0.83 (0.76-0.90)	**0.04**	81.5	80.8	47.8	95.3	80.9
Aβ42/Aβ40	p-tau181	-	0.88 (0.82-0.95)	ns	85.2	86.4	57.5	96.4	86.2
Aβ42/Aβ40	p-tau181	Age, APOE ε4	0.90 (0.85-0.96)	-	92.6	75.2	44.6	97.9	78.3

CONCLUSIONS

The use of a high reliability method for the quantification of plasma Aβ based on HPLC-MS (ABtest-MS) suggests that **plasma Aβ42/Aβ40 ratio could be a more accurate biomarker of early brain amyloid deposition** than p-tau181 in the first stages of AD.