Prediction of longitudinal cortical amyloid deposition based on CSF biomarkers for Alzheimer's disease in cognitively unimpaired individuals: the role of APOE-ε4

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Introduction

The relationship between cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease (AD), APOE-ε4 and longitudinal cortical amyloid deposition in cognitively unimpaired individuals remains unclear, but could provide novel insights in AD development and improve early AD diagnostics and trial design.

Objective

To investigate longitudinal cortical amyloid deposition on PET as predicted by baseline CSF AD biomarker profiles and APOE-ε4 carriership in cognitively unimpaired individuals.

Methods

Participants

We selected **330** cognitively unimpaired individuals from 6 European cohorts of the AMYPAD-PNH study (EPAD-LCS, ALFA+, DELCODE, FACEHBI, EMIF-AD 60++, UCL-2010-412) with available data on:

- Baseline CSF aß1-42 or Aß42/40 (A), p-tau181 (T)
- APOE-ε4 carriership (yes/no)
- Longitudinal amyloid PET

Predictors

- **AT profiles**: to evaluate different AD stages, individuals were classified as **A-T-, A-T+, A+T-**, or **A+T+** based on baseline CSF biomarker abnormality using center-specific cut-offs
- **AT profiles x APOE-ε4:** for secondary analyses, individuals were stratified based on APOE-ε4

Outcome

- Longitudinal global cortical amyloid deposition on PET (centiloids)

Statistics

Generalized linear mixed models (RI/RS) with cohort as random factor, adjusted for age and sex.

Results

Sample characteristics

- Mean age was 64+-6.1 years, 58% were female, 48% APOE-ε4 carriers. Average follow-up was 3 years. 170 individuals were A-T-, 69 A-T+, 59 A+T-, and 32 A+T+ (Table 1).

CSF AT profiles and cortical amyloid deposition on PET

- At baseline, cortical amyloid deposition was different between all groups, with A+T+ having the highest deposition, followed by A+T-, A-T+ and A-T- (Figure 1)
- Longitudinally, all groups showed increased cortical amyloid deposition, except A-T-. A+ groups showed greater increases than A- groups.

Effect of APOE-ε4

- At baseline, only in A-T+ and A+T+ groups, APOE-ε4 carriers had higher cortical amyloid deposition compared to non-carriers (Figure 2)
- Longitudinally, A-T- and A-T+ showed increased cortical amyloid deposition only if carrying APOE-ε4
  - With A-T+ showing a similar longitudinal deposition as A-T- and A-T+
- Longitudinally, A+T+ showed greater increases than A+T- in longitudinal amyloid deposition only if carrying APOE-ε4.

Table 1. Sample descriptives.

	A-T-	A-T+	A+T-	A+T+	Total sample
N	170	69	59	32	330
Age	63	65	61	67	64
Sex (F)	59%	54%	53%	67%	58%
APOE-ε4 carriership (%)	36%	42%	79%	71%	48%
Education years	15	15	15	14	15
Mean FU years	3	4	3	3	3

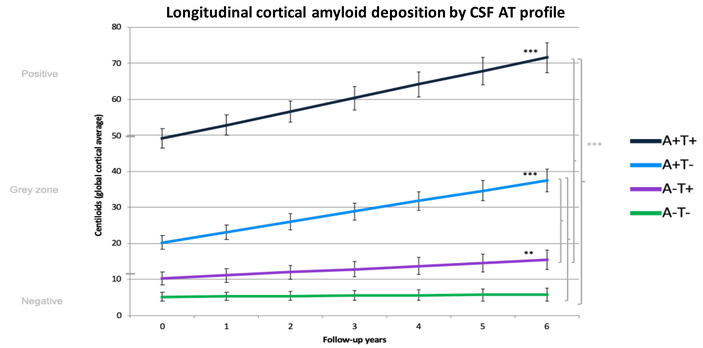

Figure 1. Linear mixed modelling slopes. Error bars represent standard errors of the mean. Slopes *** p<0.001, **p>0.005

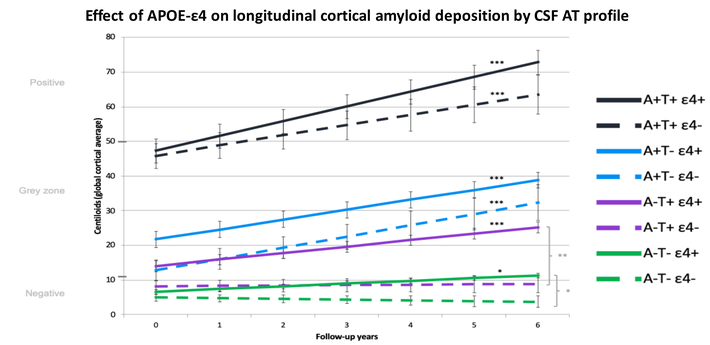

Figure 2. Linear mixed modelling slopes. Error bars represent standard errors of the mean. Slopes ***p<0.001, **p<0.005, *p<0.05.

Conclusion

APOE-ε4 impacts the association between CSF AD biomarkers and longitudinal cortical amyloid deposition on PET in cognitively unimpaired persons.

- A- APOE-ε4 carriers could be at an early AD stage, as they showed increased cortical amyloid longitudinally
- In A+ persons, p-tau abnormality related to higher baseline cortical amyloid, but only in APOE-ε4 carriers to steeper increases in cortical amyloid longitudinally

This has important implications for early diagnostics and AD clinical trial design.

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