Genetic and environmental factors are differentially related to Aβ burden in the presymptomatic phase of autosomal dominant and sporadic Alzheimer's disease

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Background and objectives

Autosomal dominant Alzheimer’s disease (ADAD) is considered the gold standard to evaluate the cascade of biomarker changes occurring in the presymptomatic phase of Alzheimer’s disease (AD), since years from symptom onset can be estimated in presymptomatic mutation carriers taking parental age at symptom onset as a reference.1 However, the presymptomatic phase of sporadic AD (sAD) is known to be influenced by environmental and genetic factors, AD pathophysiology is directly triggered by the mutation of a gene involved in beta-amyloid (Aβ) production (PSEN1, PSEN2 or APP),2 questioning the similarity of the two variants in their preclinical stage. Our objective is to evaluate whether factors known to affect Aβ trajectories in presymptomatic ADAD mutation carriers also affect asymptomatic individuals with a parental history (PH) of sAD, and vice-versa. More specifically, we want to test if parental EYO, as developed in ADAD, can help predict cerebral Aβ burden in sAD and 2) genetic and environmental factors known to affect Aβ accumulation in asymptomatic individuals at risk of sAD (apolipoproteinE4 (APOE)4 and education)5-7 also affect Aβ trajectories in presymptomatic ADAD mutation carriers.

Participants and Methods

Cognitively normal participants were recruited from the DIAN observational study, which includes children of a proband with DIAN mutation, and the PREVENT-AD cohort, which includes individuals with a PH of sAD.

Demographics

<table>
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<tr>
<th>Age (mean ± SD [range])</th>
<th>Sex [M:F]</th>
<th>EYO [mean ± SD [range]]</th>
<th>Education [mean ± SD [range]]</th>
<th>APOE carriers [%]</th>
<th>PSEN1/PSEN2/APP [%]</th>
<th>Aβ SUVR [mean ± SD [range]]</th>
<th>Aβ positive [%]</th>
<th>MMSE [mean ± SD [range]]</th>
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“Estimated Years from expected symptom Onset” (EYO) calculation

For all individuals we calculated an EYO as follows: participant’s age – parental age at symptom onset

Imaging

All participants underwent structural MRI and Aβ-PET scans. T1-weighted images were acquired following ADNI protocol, on different MRI scanners for DIAN (due to the multicenter nature of the study), and on a Siemens 3T scanner for the PREVENT-AD. 30-minute Aβ-PET scans were acquired ~40 minutes after the intravenous injection of 8 to 18 mCi of Ci89MIBF tracer for DIAN participants and 0.5-4mCi of F18-florbetapir in PREVENT-AD cohort.

PET processing

Images were preprocessed using SPM and Acpet: MNI standard automated cortical parcellation template, 40-TesLA acquisition, SPM8 (v6.9), FMRIB Software Library, and Python packages for nifti data analysis.

Analyses

1) We assessed the effect of EYO on Aβ burden in both cohorts using partial correlations, controlling for age and sex (site and mutation type in ADAD).
2) We assessed the effect of APOE status, education, and their interaction on Aβ burden in both cohorts using general linear models, controlling for age, sex and MMSE (site and mutation type in ADAD).

Analyses were replicated osseous using SPM12.

Results

1) Can a parental EYO, as developed in ADAD, predict cerebral Aβ burden in preclinical sAD?

In preclinical ADAD mutation carriers, Aβ burden is not affected by APOE status. It decreases as years of education increase.

2) Do factors known to affect Aβ accumulation in asymptomatic individuals at risk of sAD (i.e. APOE4 and education) also affect Aβ trajectories in preclinical ADAD mutation carriers?

In asymptomatic individuals with a PH of sAD, Aβ burden is higher in APOE4 carriers than in non-carriers, and it decreases as a function of years of education.

Summary and conclusions

Our results suggest that, as it is the case in ADAD, a parental EYO index might help to predict Aβ accumulation in asymptomatic individuals at risk of sAD.2,8 This might have important implications for the characterization of the presymptomatic phase of AD and the recruitment of prevention/clinical trials.

While APOE4 is highly associated with Aβ burden in people at risk of sAD, it has no impact in ADAD. By contrast, environmental factors, approximated here using years of education, could affect biomarker progression in both variants of the disease. Furthermore, education seems able to counteract the deleterious effect of Aβ on Aβ burden in asymptomatic individuals with a PH of sAD.5,7 These results suggest the existence of reserve mechanisms, not only in individuals carrying aggressive ADAD variants.