Continuous β-Amyloid CSFPET Imbalance Model to Capture Alzheimer Disease Heterogeneity

Mastenbroek SE, Sala A, Vállez García D, Shekari M, Salvadó G, Lorenzini L, Pieperhoff L, Wink AM, Lopes Alves I, Wolz R, Ritchie C, Boada M, Visser PJ, Bucci M, Farrar G, Hansson O, Nordberg AK, Ossenkoppele R, Barkhof F, Gispert JD, Rodriguez-Vieitez E, Collij LE, ADNI, AMYPAD consortium

Abstract:

Background and objectives: Discordance between CSF and PET biomarkers of β-amyloid (Aβ) might reflect an imbalance between soluble and aggregated species, possibly reflecting disease heterogeneity. Previous studies generally used binary cutoffs to assess discrepancies in CSF/PET biomarkers, resulting in a loss of information on the extent of discordance. In this study, we (1) jointly modeled Aβ-CSF/PET data to derive a continuous measure of the imbalance between soluble and fibrillar pools of Aβ, (2) investigated factors contributing to this imbalance, and (3) examined associations with cognitive trajectories.

Methods: Across 822 cognitively unimpaired (n = 261) and cognitively impaired (n = 561) Alzheimer's Disease Neuroimaging Initiative individuals (384 [46.7%] females, mean age 73.0 ± 7.4 years), we fitted baseline CSF-Aβ42 and global Aβ-PET to a hyperbolic regression model, deriving a participant-specific Aβ-aggregation score (standardized residuals); negative values represent more soluble relative to aggregated Aβ and positive values more aggregated relative to soluble Aβ. Using linear models, we investigated whether methodological factors, demographics, CSF biomarkers, and vascular burden contributed to Aβ-aggregation scores. With linear mixed models, we assessed whether Aβ-aggregation scores were predictive of cognitive functioning. Analyses were repeated in an early independent validation cohort of 383 Amyloid Imaging to Prevent Alzheimer's Disease Prognostic and Natural History Study individuals (224 [58.5%] females, mean age 65.2 ± 6.9 years).

Results: The imbalance model could be fit (pseudo-R2 = 0.94) in both cohorts, across CSF kits and PET tracers. Although no associations were observed with the main methodological factors, lower Aβ-aggregation scores were associated with larger ventricular volume (β = 0.13, p < 0.001), male sex (β = −0.18, p = 0.019), and homozygous APOE-ε4 carriership (β = −0.56, p < 0.001), whereas higher scores were associated with increased uncorrected CSF p-tau (β = 0.17, p < 0.001) and t-tau (β = 0.16, p < 0.001), better baseline executive functioning (β = 0.12, p < 0.001), and slower global cognitive decline (β = 0.14, p = 0.006). In the validation cohort, we replicated the associations with APOE-ε4, CSF t-tau, and, although modestly, with cognition.

Discussion: We propose a novel continuous model of Aβ CSF/PET biomarker imbalance, accurately describing heterogeneity in soluble vs aggregated Aβ pools in 2 independent cohorts across the full Aβ continuum. Aβ-aggregation scores were consistently associated with genetic and AD-associated CSF biomarkers, possibly reflecting disease heterogeneity beyond methodological influences.

Published online: 11 June 2024

Neurology

https://doi.org/10.1212/WNL.0000000000209419

Download the PDF here.