Appropriateness of Applying CSF Biomarker Cutoffs from Alzheimer's Disease to Parkinson's Disease

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Motivations

- Cutoff analysis for abnormal levels of CSF biomarkers exists in AD: $A\beta$ 1-42, t-tau, p-tau, t-tau / $A\beta$ 1-42, p-tau / $A\beta$ 1-42.
- Studies of biological relevant cutoffs for PD are limited.
- Direct assessment of the applicability of AD CSF biomarker cutoffs to predict AD neuropathology in living patients with PD has not made.

Research Objectives

- Assess the suitability and diagnostic accuracy of established AD-derived CSF biomarker cutoffs in the PD population.

The study is based on **two** metrics:

1. Baseline and longitudinal cognitive impairment.
2. Positron emission tomography (PET) amyloid imaging.

Data Description

- **Data source:** Parkinson's Progression Markers Initiative (PPMI) study—An observational multicenter study identifying PD biomarkers.
- **Data collection:** Downloaded from `www.ppmi-info.org` on June 1st, 2020.
- **Cohort formation:** 423 participants in PD cohort and 196 participants in healthy cohort (HC).
- **Data structure:** baseline CSF measures and clinical data with annual follow up visits at year 1, 2, 3, 4, 5 (longitudinal).
- **PD cohort:** Each participant has a PD diagnosis and a positive dopamine transporter (PDT) SPECT
- **PD diagnosis duration:** Average of 6.7 (sd 6.5) months

Clinical Data Measures

Two cognitive impairment measures:

1. Montreal Cognitive Assessment (MoCA) adjusted for education, and then discretized:
   - Moca ≥ 26: cognitively normal
   - MoCA < 26: cognitively impaired
2. Clinical diagnosis of cognitive state according to the Movement Disorder Society (MDS) Task Force Level I criteria
   - Normal cognition (NC)
   - Mild cognitive impairment (MCI)
   - PD with dementia (PDD)

CSF Analysis

Standard PPMI protocol (for CSF biospecimens collection): Levels of $A\beta$ 1-42, t-tau and p-tau were measured using Elecsys® electrochemiluminescence immunoassays on the cobas e 601 analysis platform (Roche Diagnostics).
Notice: Pre-analytical factors in specimen collection and analysis across studies can influence CSF $A\beta$ 1-42 levels.
Solution: Convert the Elecsys values to AlzBio3 equivalents using

$$(\text{CSF}A\beta\text{1-42} + 251.55)/3.74,$$

with cutoff AlzBio3 < 250 pg/ml (amyloid positive).

PET Analysis

- A sample of 34 patients underwent PET imaging for 18F-Flobetaben (FBB).
- FBB measurements of quantitative standardized uptake value ratio (SUVr) values were compared to the global cerebellar reference region cutoff: ≥ 1.48, indicating pathologically amyloid beta positive.

Notice: Only 22 patients with $A\beta$ 1-42 measurements underwent PET imaging at the same visit.
Solution: We took their Elecsys measurements of $A\beta$ 1-42 within one year before or after PET imaging.

Statistical Methodologies

- Analyze the cross-sectional relationship between the three CSF biomarkers and the two cognitive impairment outcomes at baseline: logistic regression analysis using univariate and multivariate models
- Evaluate the association between baseline CSF biomarkers and longitudinal incident cognitive impairment: generalized estimating equation (GEE)
- Compare univariate and multivariate models: DeLong's test for determining the significance between the area under the curve (AUC) values of the receive operating characteristic (ROC) curves
- Calculate optimal cutoff: leave-one-out cross validation based on Youden's index
- Obtain optimal cutoff confidence interval (CI): stratified bootstrapping

Analysis Results of PPMI study

Optimal Cutoffs and AUC values for $A\beta$ 1-42 (multivariate model)

	dx	moca26	PET
AD cutoff	683	683	683
AUC, AD cutoff (SE)	0.737 (0.015)	0.690 (0.012)	0.696 (0.137)
Opt cutoff (CI)	710 (635, 725)	1162 (523, 1338)	945 (927, 1057)
AUC, Opt cutoff (SE)	0.744 (0.015)	0.690 (0.012)	0.756 (0.093)
P-value	0.1	0.7	0.7

Analysis Results of PPMI study (cont'd)

Optimal Cutoffs and AUC values for T-tau $/A\beta$ 1-42 (multivariate model)

	dx	moca26	PET
AD cutoff	0.27	0.27	0.27
AUC, AD cutoff	0.728	0.678	0.689
AUC, AD cutoff SE	0.025	0.017	0.146
Opt cutoff	0.215	0.219	0.178
Opt cutoff CI	(0.191, 0.344)	(0.160, 0.318)	(0.136, 0.259)
AUC, Opt cutoff	0.725	0.680	0.778
AUC, Opt cutoff SE	0.025	0.017	0.087
P-value	0.8	0.5	0.4

Optimal Cutoffs and AUC values for P-tau $/A\beta$ 1-42 (multivariate model)

	dx	moca26	PET
AD cutoff	0.025	0.025	0.025
AUC, AD cutoff	0.736	0.669	0.704
AUC, AD cutoff SE	0.026	0.018	0.125
Opt cutoff	0.018	0.016	0.019
Opt cutoff CI	(0.016 0.029)	(0.013, 0.029)	(0.012, 0.023)
AUC, Opt cutoff	0.732	0.670	0.793
AUC, Opt cutoff SE	0.025	0.018	0.129
P-value	0.7	0.8	0.6

Discussions

- The cutoffs for CSF biomarkers to predict both cognitive impairment and PET amyloid in this PD cohort are significangtly from those established in AD patients.
- PD-specific cutoffs to predict cognitive decline and cerebral amyloidosis for use in PD cohorts need to be defined and independently validated.
- PD pathology may partially suppress the increasing levels of t-tau and p-tau seen in AD, and p-tau may predict progression to cognitive impairment in binary models.

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