Title

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Journal

Alzheimer's & Dementia, 20(Suppl 2)

ISSN

1552-5260

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Publication Date

2024-12-01

DOI

10.1002/alz.091273

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BIOMARKERS

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BIOMARKERS (NON-NEUROIMAGING)

ATN_{PD} to improve detection of concomitant Alzheimer's pathology in autopsy-confirmed Parkinson's disease

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Abstract

Background: In Parkinson's disease (PD), concomitant Alzheimer's disease (AD) pathologic change (ADNC) is common and results in altered motor and cognitive phenotypes. However, detection of PD with AD (PD+AD) using biofluid markers is challenging. While decreased cerebrospinal fluid (CSF) β-amyloid 1-42 ($A\beta_{42}$) strongly reflects β-amyloid burden, PD subjects typically harbor lower CSF phosphorylated tau 181 ($p\text{-}tau_{181}$) and total tau (t-tau) levels than healthy controls, which complicates detection of tau tangles and neurodegeneration. We previously tested PD-specific application of the β-amyloid/tau/neurodegeneration framework (ATN_{PD}); combining CSF $A\beta_{42}$, CSF $p\text{-}tau_{181}$, and serum neurofilament light (NfL) in a living PD cohort. ATN_{PD}, using a lower CSF $p\text{-}tau_{181}$ cutpoint, predicted cognitive decline. However, ATN_{PD} cutpoints still must be validated against autopsy assessments of ADNC as gold-standard. Here, we compare biomarker strategies in all available autopsy-confirmed PD from the Parkinson's Progression Markers Initiative (PPMI).

Methods: Eighteen PD participants with autopsy-confirmed Lewy body disease and antemortem biofluid were available for analysis (Table 1). PD+AD included high/intermediate ADNC (n=9); PD without AD (PD; n=9) included not/low ADNC. Cerebral cortical atrophy determined neurodegeneration (mild/moderate vs. none). CSF was assayed for $A\beta_{42}$ (n=14), $p\text{-}tau_{181}$ (n=17), and t-tau (n=17) using Roche cobas e 601; $p\text{-}tau_{181}/A\beta_{42}$ and $t\text{-}tau_{181}/A\beta_{42}$ ratios were calculated. Serum NfL was assayed using Simoa Quanterix (n=18). Biofluid measurements closest to autopsy were selected. Receiver operating characteristic (ROC) analyses with bootstrapping tested discrimination of PD+AD from PD using CSF biomarkers, and of neurodegeneration from not using CSF t-tau and serum NfL.

Results: ROC cutpoints for CSF $A\beta_{42}$, $p\text{-}tau_{181}$, and serum NfL were equivalent to ATN_{PD} cutpoints, while $p\text{-}tau_{181}$ and t-tau were lower than published AD-cutpoints (Table 2). CSF $p\text{-}tau_{181}/A\beta_{42}$, $t\text{-}tau_{181}/A\beta_{42}$, $A\beta_{42}$ and serum NfL had high area under the

curve (AUC>0.80; Table 2A,2B). In contrast, CSF p-tau$_{181}$ and t-tau demonstrated poor discrimination (Table 2A) and no difference between groups (Table 1), potentially due in part to low sample size. A chi-square test confirmed classification is improved using ATN$_{PD}$ and AD-cutpoints (χ^2=14, p=0.0015; Figure 1).

Conclusions: PD-specific biomarker strategies/cutpoints are needed to maximize detection of concomitant ADNC, but must be validated in larger autopsy cohorts.

Demographic Characteristics	Not	ADNC	p
n	9	9	
Age at CSF (years)	67.10 [61.55, 73.73]	71.80 [64.60, 73.70]	0.441
Age at serum (years)	70.90 [65.70, 76.50]	74.30 [68.90, 75.70]	0.627
Age at Onset (years)	66.65 [56.11, 70.92]	64.61 [61.17, 68.99]	1.000
Age at Death (years)	74.00 [69.00, 78.00]	75.00 [74.00, 80.00]	0.451
Survival (years)	10.10 [9.20, 10.91]	10.89 [6.32, 12.06]	0.674
MoCA	26.00 [24.00, 28.00]	26.00 [25.00, 27.00]	0.638
Sex = Male (%)	6 (66.7%)	6 (66.7%)	1.000
Race = White (%)	9 (100.0%)	9 (100.0%)	--
APOE ε4 = 1 or 2 (%)	2 (22.2%)	4 (44.4%)	0.617
GBA+ (%)	2 (22.2%)	2 (22.2%)	1.000
LRRK2+ (%)	1 (11.1%)	1 (11.1%)	1.000
ADNC (%)			<0.001
Not	3 (33.3%)	0 (0.0%)	
Low	6 (66.7%)	0 (0.0%)	
Intermediate	0 (0.0%)	6 (66.7%)	
High	0 (0.0%)	3 (33.3%)	
Braak Score (%)			0.007
0	1 (11.1%)	0 (0.0%)	
1	6 (66.7%)	0 (0.0%)	
2	2 (22.2%)	6 (66.7%)	
3	0 (0.0%)	3 (33.3%)	
Lewy Body Braak = 6 (%)	7 (77.8%)	8 (88.9%)	1.000
CSF Aβ42	849.00 [743.00, 1116.00]	469.00 [402.50, 606.00]	0.025
CSF p-tau181	12.50 [11.75, 14.50]	13.00 [11.00, 19.00]	0.846
CSF t-tau	160.00 [138.25, 183.50]	164.00 [130.00, 225.00]	0.773
CSF p-tau/Aβ42	0.015[0.013, 0.016]	0.021[0.019, 0.038]	0.013
CSF t-tau/Aβ42	0.18 [0.16, 0.22]	0.27 [0.24, 0.43]	0.018
Serum NfL	18.00 [12.00, 27.00]	25.00 [18.00, 30.00]	0.101

Table 1: Demographics of PD with AD co-pathology (PD+AD; high/intermediate ADNC) and without (PD; not/low ADNC). For continuous variables, median and interquartile range (IQR) are reported; Wilcoxon tests performed group comparisons. For categorical variables, count (percentage [%]) are provided; chi-square tests performed frequency comparisons. *p*-values are reported for group comparisons.

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A. PD+AD vs. PD	AUC	AUC 95% CI	Threshold	Threshold 95% CI	Sensitivity	Specificity	Accuracy
CSF p-tau/Aβ42	0.90	0.69 -- 1.00	0.018	0.015 -- 0.025	0.78	0.83	0.81
CSF t-tau/Aβ42	0.88	0.65 -- 1.00	0.24	0.20 -- 0.31	0.78	0.84	0.81
CSF Aβ42	0.86	0.61 -- 1.00	656.41	515.04 -- 852.90	0.82	0.85	0.83
CSF t-tau	0.54	0.26 -- 0.82	173.44	125.81 -- 205.02	0.53	0.66	0.59
CSF p-tau	0.53	0.24 -- 0.81	14.36	9.91 -- 17.24	0.50	0.70	0.59
B. Atrophy vs. none	AUC	AUC 95% CI	Threshold	Threshold 95% CI	Sensitivity	Specificity	Accuracy
Serum NfL	0.92	0.72 -- 1.00	19.622	17.00 -- 23.42	0.82	0.89	0.84
CSF t-tau	0.60	0.25 -- 0.91	160.572	122.46 -- 214.62	0.59	0.65	0.61

Table 2: ROC analyses. Testing biofluid markers (A.) of amyloid and tau to discriminate high/intermediate ADNC from not/low ADNC, and (B.) of neurodegeneration to discriminate mild/moderate cortical atrophy from none. ROC metrics were calculated using bootstrapping with 2000 iterations: AUC, threshold, 95% confidence intervals [95%CI]. Youden's index determined best threshold; sensitivity, specificity, and accuracy are calculated at threhold. ATN_{PD} cutpoints are CSF Aβ42≤683 (Weinshel *et al.*, 2022), CSF p-tau_{181}>=13 (Weinshel *et al.*, 2022), and serum NfL>=19.05 (Cousins *et al.*, 2024). AD-derived cutpoints are CSF Aβ42≤683 to account for PPMI analytical factors (Weinshel *et al.*, 2022), and p-tau_{181}≥24 and t-tau≥266 (Blennow *et al.*, 2019).

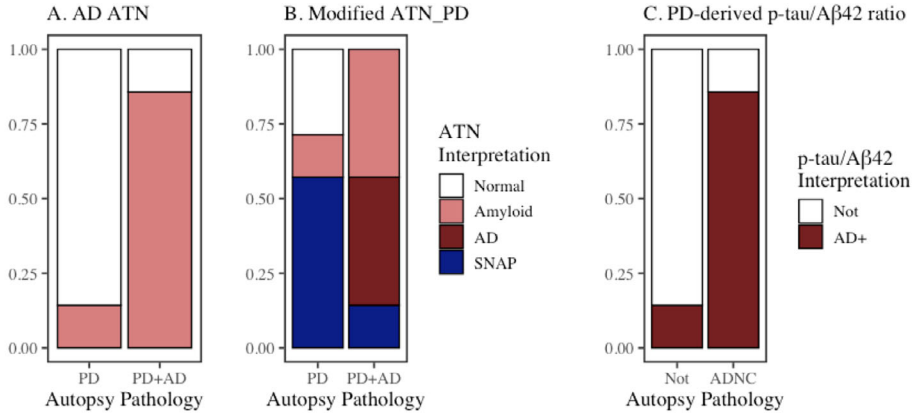

Figure 1: Classifications of PD by biomarker strategies. Classification proportions of PD over time by (A.) AD-based ATN, (B.) modified ATN_{PD}, and (C.) PD-derived p-$tau_{181}/A\beta_{42}$ ratio. Color indicates (A.) ATN and (B.) ATN_{PD} interpretation: Normal (white; A-T-N-), Amyloid (coral; A+T-N-), AD (A+T+N±), and suspected non-Alzheimer's pathology (SNAP) (blue; A-T±N±). For ATN, correct classification of PD is "SNAP" (blue), and of PD+AD is "AD" (red). For p-$tau_{181}/A\beta_{42}$ ratio, correct classification of PD is "Not" (white), and of PD+AD is "AD+" (red).