Association Between CSF Biomarkers and Clinical Phenotype of Early Parkinson's Disease in the Parkinson's Progression Markers Initiative (PPMI)

Ju-Hee Kang,[1] Chelsea Caspell,[2] Chris Coffey,[2] Peggy Taylor,[3] Mark Frasier,[4] Kenneth Marek,[5] John Q Trojanowski,[1] Leslie M Shaw[1]

[1]Department of Pathology, Perelman School of Medicine, University of Pennsylvania, PA; [2]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA; [3]Covance, Dedham, MA, [4]The Michael J. Fox Foundation for Parkinson's Research, New York, NY; [5]Institute for Neurodegenerative Disorders, New Haven, CT

BACKGROUND and OBJECTIVE

There is substantial heterogeneity in the onset and progression of clinical phenotypes of Parkinson's disease (PD) such as cognitive impairment, a common non-motor complication that progresses to overt dementia in ~80% of PD patients with long standing disease. The PPMI is an ongoing international multicenter study to assess progression of clinical features, imaging and biochemical biomarkers in *de novo* PD compared to healthy controls (HC) and in PD subtypes. The purpose of this study was to explore the association of baseline CSF biomarkers ($A\beta_{1-42}$, t-tau, p-tau_{181} and α-synuclein) with clinical features in *de novo* drug-naive PD patients enrolled in the PPMI study.

SUBJECTS and METHODS

Subjects: Baseline CSF samples were obtained from 106 individuals (39 HC, 63 PD patients, and 4 subjects without evidence of dopamine deficit (SWEDD)) at the time the subjects entered PPMI. Demographics, H&Y stage, UPDRS, smell test (UPSIT) score, neuropsychological and cognitive assessments, CSF hemoglobin (CSF Hgb) level and dopamine transporter (DaT) scan were evaluated.

Analysis of CSF & Quality control samples: CSF $A\beta_{1-42}$, t-tau and p-tau_{181} were measured using the research-use-only multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with INNOBIA Alz-Bio3 immunoassay kits (Fugireibio-Innogenetics, Belgium), and CSF α-synuclein (α-syn) was measured by ELISA. All standards, QC aqueous controls and CSF samples (including 2 CSF pools for run validation) were analyzed in duplicate in each run.

Statistical analysis: To assess differences between groups, the Mann-Whitney U test was used. To explore the association between biomarkers and clinical factors, we used multivariate regression models after adjustment for confounding factors. Chi-square test was used to test for gender difference or comparing proportion of subjects with CSF Hgb contamination.

RESULTS

Table 2. Comparison of CSF biomarker levels between HC and PD patients.

Biomarkers	HC (N = 39)	PD (N = 63)	SWEDD (N = 4)
$A\beta_{1-42}$ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)	228.7 ± 45.63 (217.2 – 240.2)*	276.0 ± 22.99
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)*	55.0 ± 25.47
p-tau_{181} (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)**	23.5 ± 8.35
t-tau/$A\beta_{1-42}$	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)*	0.196 ± 0.083
p-tau_{181}/$A\beta_{1-42}$	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.084 ± 0.023
p-tau_{181}/t-tau	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.495 ± 0.230
α-syn (pg/mL)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)*	1413 ± 750.6

*Data are mean ± S.D. (95% Confidence Interval) #Mann-Whitney U test for the comparison between HC and PD.

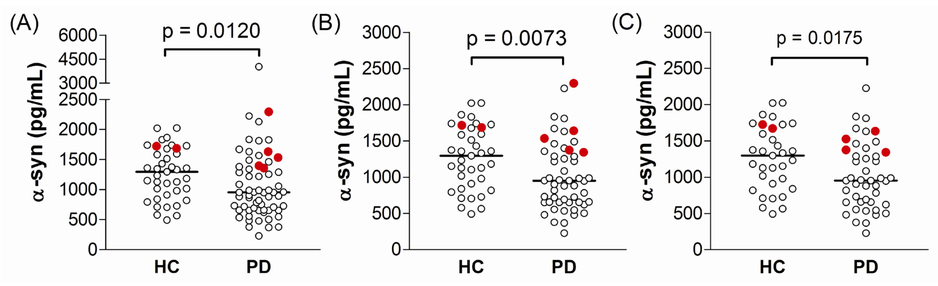


Fig. 1. Scatter plots of CSF α-syn concentrations in HC and PD. We differentiated each group according to their CSF Hgb concentration to (A) total subjects, (B) Subjects with CSF Hgb < 500 ng/mL, and (C) Subjects with CSF Hgb < 200 ng/mL. Red dots indicate subjects with AD-like CSF biomarker signature.

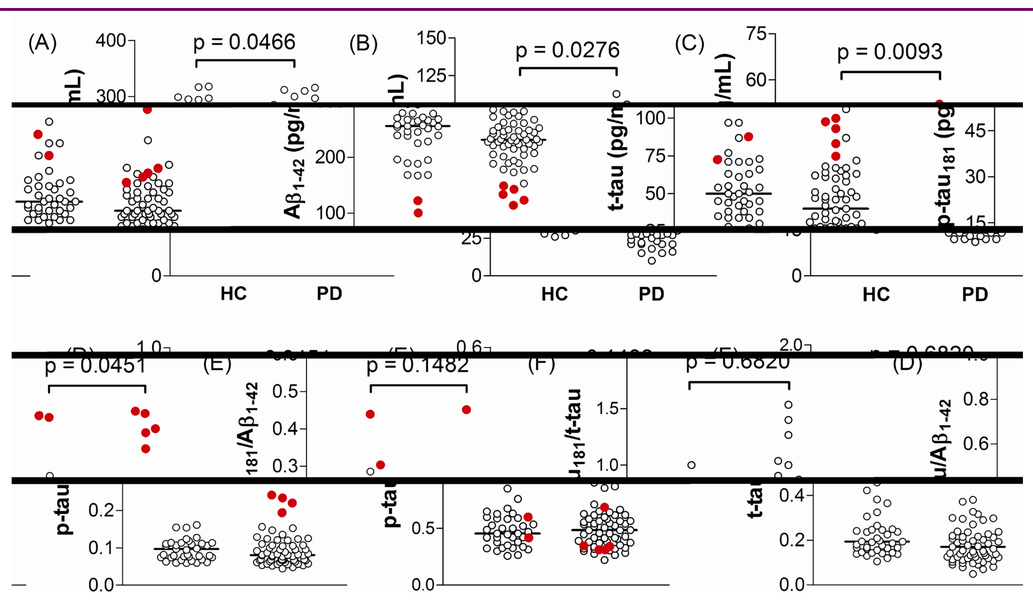
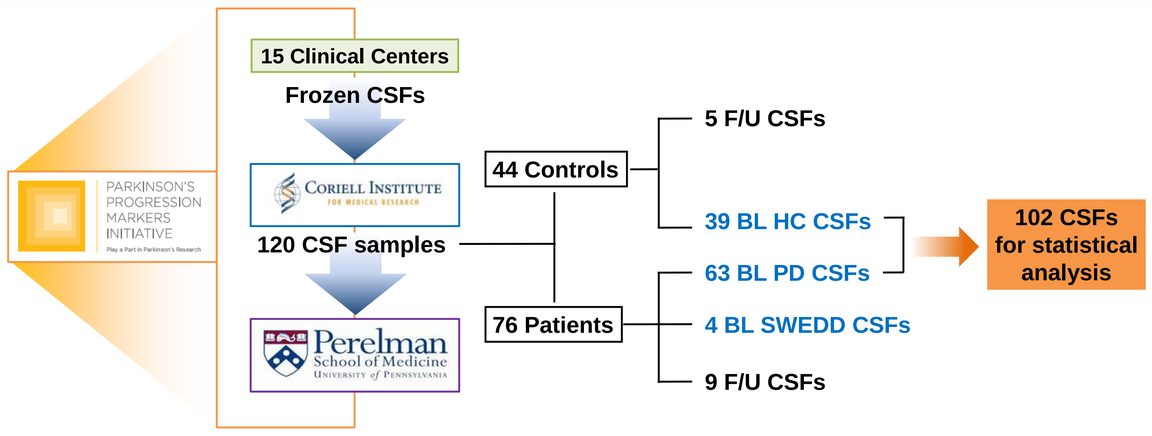


Fig. 2. Scatter plots of AD CSF biomarkers (A-C) and their ratios (D-F) in HC and PD. Red dots indicate subjects with AD-like CSF biomarker signature with low Aβ1-42 and high t-tau. These individuals were selected using Grubb's test of t-tau/$A\beta_{1-42}$ ratio, and showed significantly lower olfactory function score compared to other PD patients (N=58, p = 0.0245)

- Using multiple logistic regression modeling with stepwise selection method, we found that lower CSF α-syn was significantly associated with a higher odds of PD diagnosis at baseline visit (p = 0.0019).
- Decreased CSF p-tau_{181} level was associated with increased UPDRS III motor score (multiple linear regression model, p = 0.0140).
- When we classified PD patients with their motor phenotypes to tremor-dominant (TD) or postural instability-gait disturbance (PIGD)-dominant type, lower CSF $A\beta_{1-42}$ levels were significantly associated with PIGD-dominant phenotype (p = 0.0352). PIGD were previously shown to experience more rapid cognitive decline compared to TD patients.



RESULTS

Table 1. Comparison of demographic and clinical parameters between HC and PD.

	HC (N = 39)	PD (N = 63)	SWEDD¶ (N = 4)
Age, yr (95% C.I.)	59 ± 13 (55 – 63)	62 ± 10 (60 – 65)	67 ± 7 (55 – 78)
Sex, F/M (% of Male)	18/21 (53.8)	26/39 (61.9)	2:2 (50.0)
Education, yr (95% C.I.)	16.9 ± 2.4 (16.1 – 17.6)	16.4 ± 2.5 (15.8 – 17.0)	14.3 ± 2.1 (11.0 – 17.5)
Mean age of onset, yr (95% C.I.)	-	59.5 ± 10.8 (56.8 – 62.2)	63.5 ± 8.2 (50.5 – 76.5)
Median duration of Sx.	-	1.8 years	2.0 years
No. of subjects with CSF Hgb > 200 ng/mL	6 (15.4%)	18 (28.6%)	1 (25.0%)
H & Y	0.03 ± 0.16	1.65 ± 0.51****	1.50 ± 0.58
UPDRS III score	1.6 ± 2.7	22.6 ± 7.6****	17.3 ± 6.2
Mean tremor core	0.05 ± 0.13	0.46 ± 0.27****	0.50 ± 0.20
Mean PIGD score	0.01 ± 0.04	0.24 ± 0.26****	33.0 ± 2.9
UPSIT score	35.1 ± 3.4	21.9 ± 8.1****	33.0 ± 2.9
MoCA score	28.4 ±1.0	27.2 ± 2.0**	27.3 ± 2.4
Semantic fluency	53.8 ± 12.1	49.5 ± 10.6	40.8 ± 4.1
WMSIII-LNS score	12.1 ± 2.8	11.0 ± 2.0	10.0 ± 1.4
SDMT	48.6 ± 11.2	41.9 ± 8.9**	44.8 ± 7.7
HVLT_total recall	9.0 ± 1.6	8.2 ± 1.5**	7.8 ± 2.4
HVLT delayed recall	9.9 ± 2.3	8.3 ± 2.3***	9.3 ± 4.2

Mean Striatal binding ratios	PR	PL	CR	CL	PR	PL	CR	CL	PR	PL	CR	CL
	1.38	1.39	2.06	2.05	0.61	0.64	1.34	1.33	1.39	1.56	2.00	2.02

#Data are mean ± S.D. **p < 0.01, ***p < 0.001, ****p < 0.0001 versus HC; determined by the Mann-Whitney U test .
¶Abbreviations: SWEDD: Subjects Without Evidence of Dopamine Deficit, H & Y: Hoehn & Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale, UPSIT: University of Pennsylvania Smell Identification Test, MocA: Montreal Cognitive Assessment, WMSIII-LNS: Wechsler Memory Scale III Letter-Number Sequencing, SDMT: Symbol Digit Modalities Test, HVLT-R: Hopkins Verbal Learning Test-Revised, PL and PR: Putamen Right and Putamen Left, CR and CL: Caudate Right and Caudate Left.

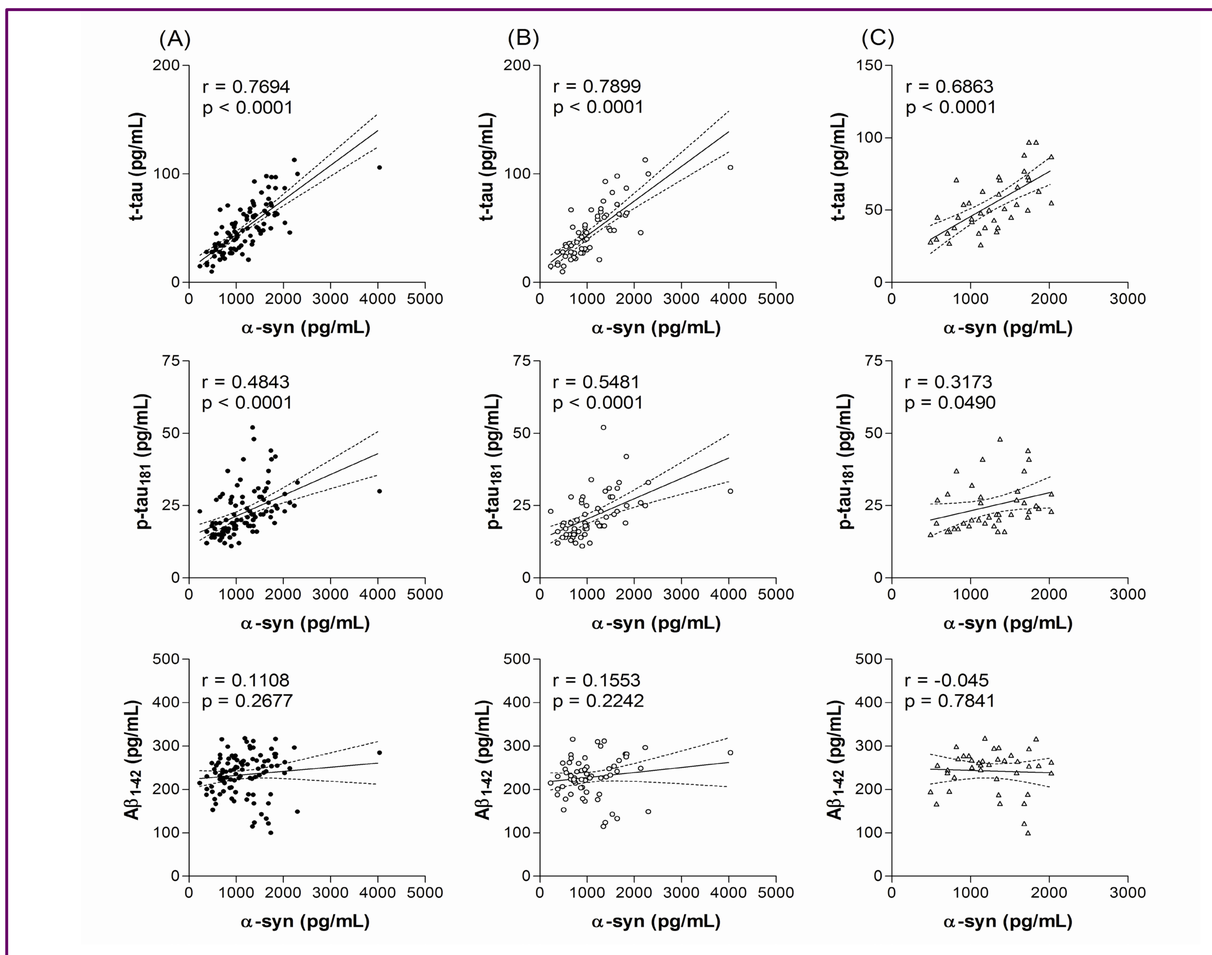


Fig. 3. Correlation of CSF α-syn level with AD CSF biomarkers in (A) total of 102 subjects, (B) 63 PD patients and (C) 39 healthy controls. Solid lines and dotted lines indicate linear regression and 95% confidence intervals, respectively.

CONCLUSIONS

1) We found that the level of CSF $A\beta_{1-42}$, t-tau and p-tau_{181}, and α-syn of PD patients were significantly lower than those of HC.
2) Lower CSF α-syn was significantly associated with a higher odds of PD diagnosis.
3) CSF α-syn level was significantly correlated with the concentration of CSF tau proteins.
4) We detected a subgroup of PD with AD-like CSF signature that had significantly lower olfactory function score compared to other PD patients.
5) Lower CSF $A\beta_{1-42}$ levels were associated with PIGD-dominant motor phenotype.
6) Further investigations are planned to test the predictive performance of the biomarkers for disease progression.

ACKNOWLEDGEMENT : This study was supported by Michael J. Fox Foundation