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

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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 motor complication that progresses to overt dementia in ~80% of PD patients with long standing disease. The PPMI is an ongoing international multi-center study to assay 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 (Aβ42, t-tau, p-tau181 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&V stage, UPDRS, smell test (UPSIT) score, neuropsychological and cognitive assessments, CSF hemoglobin (CSF Hb) level and dopamine transporter (DaT) scan were evaluated.

Analysis of CSF & Quality control samples: CSF Aβ42, t-tau and p-tau181 were measured using the research-use-only multiplex LMAP Luminex platform (Luminex Corp, Austin, TX) with INNObio Alpha-Biolo immunoassay kits (Fugiregio-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 statistical analysis:

RESULTS

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

CONCLUSIONS

1) We found that the level of CSF Aβ42, t-tau and p-tau181, and α-syn of PD patients were significantly lower than those of HC.

2) Lower CSF α-syn level 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 Aβ42 levels were associated with PDGFB-dominant motor phenotype.

6) Further investigations are planned to test the predictive performance of the biomarkers for disease progression.

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

Fig. 1. Scatter plots of CSF α-syn levels 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 ≥ 500 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 Aβ42 and high t-tau). These individuals were selected using Glueb’s test of t-tau/Aβ42 ratio, and showed significantly lower olfactory function score compared to other PD patients (N=58, p = 0.0245).

Fig. 3. Correlation of CSF α-syn level with AD-like CSF biomarker signature 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.

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-tau181 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 Aβ42 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.

1 Data are means ± SD. (95% Confidence Intervals) Minitab t-test was used for the comparison between HC and PD.

2 Two-tailed t-test for the comparison between HC and PD.

3 Mann-Whitney U test.

4 T-test with Bonferroni correction.

5 χ2 test for the comparison between HC and PD.

**p < 0.01, ***p < 0.001, ****p < 0.0001 versus HC, determined by the Mann Whitney U test.

6 We used the non-parametric Kruskal-Wallis test. All continuous variables were compared using the Mann-Whitney U test.

7 We included subjects without evidence of Dopamine Deficit, A & B & H&V stage, PDGFB (LSP4) variant, and PPMI-UPSRT (University of Pennsylvania level-identified Test, Modified Motor Cognitive Assessment, MFAQ-UPSRT, Wechsler Memory Scale, Dr. H&V Letter

8 The number of patients is approximately 30 patients, 53.1% with a total of 102 patients, 63 PD patients, and 39 healthy subjects.

9 1st Mean Striatal binding ratios (50%); 2nd Mean Striatal binding ratios (50%); 3rd Mean Striatal binding ratios (50%)