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Evolution of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in Early Parkinson's Disease

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Abstract

Objective: We analyzed the longitudinal profile of Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers in early Parkinson's disease (PD) compared with healthy controls (HC) and tested baseline CSF biomarkers for prediction of clinical decline in PD.

Methods: Amyloid-β ($A\beta_{42}$), total tau (t-tau) and tau phosphorylated at the threonine 181 position (p-tau) were measured using the high-precision Roche Elecsys® electrochemiluminescence immunoassay in all available CSF samples from longitudinally studied PD (n=416) and HC (n=192) followed for up to three years in the Parkinson's Progression Markers Initiative (PPMI). Longitudinal CSF and clinical data were analyzed with linear-mixed effects models.

Results: We found PD patients had lower CSF t-tau (median=157.7pg/mL,range=80.9–467.0), p-tau (median=13.4pg/mL,range=8.0–40.1) and $A\beta_{42}$ (median=846.2pg/mL,range=238.8–3707.0) than HC at baseline (CSF t-tau median=173.5pg/mL,range=82.0–580.8; p-tau median=15.4pg/mL,range=8.1–73.6; $A\beta_{42}$ median=926.5pg/mL,range=239.1–3297.0;p<0.05–0.001) and a moderate-to-strong correlation among these biomarkers in both PD and HC (Rho=0.50–0.97; p<0.001). 31.5% of PD had pathologically-low levels of CSF $A\beta_{42}$ baseline and these PD patients had lower p-tau levels (median=10.8pg/mL, range=8.0–32.8) compared to 27.7% of HC with pathologically-low CSF $A\beta_{42}$ (CSF p-tau median=12.8pg/mL, range 8.2–73.6;p<0.03). In longitudinal CSF analysis, we found PD had greater decline in CSF $A\beta_{42}$ (mean difference= −41.83 pg/ml; p=0.03) and CSF p-tau (mean difference= −0.38 pg/ml; p=0.03) at year three compared to HC. Baseline CSF $A\beta_{42}$ values predicted small but measurable decline on cognitive, autonomic and motor function in early PD.

Interpretation: Our data suggest baseline CSF AD biomarkers may have prognostic value in early PD and that the dynamic change of these markers, while modest over a three-year period, suggest biomarker profiles in PD may deviate from healthy aging.

Keywords

Parkinson's disease; Alzheimer's disease; biomarker; cerebrospinal fluid; tau; amyloid-beta; PPMI; alpha-synuclein

INTRODUCTION

There is significant clinical and pathological heterogeneity of Parkinson's disease (PD), and while α-synuclein (aSyn) Lewy pathology and the associated synapse and neuronal loss is the hallmark of this disease, there is varying severity of mixed Alzheimer's disease (AD) associated amyloid-beta ($A\beta_{42}$) plaques and tau tangles found at autopsy in many PD patients. Indeed, approximately 30% of autopsy-confirmed PD have sufficient postmortem

plaque and tangle pathology to meet neuropathologic criteria for a second diagnosis of AD, and these patients have a more rapid decline in cognition and overall survival than PD patients with minimal AD co-pathology[1, 2]. Thus, identifying markers of AD pathology during life may have important prognostic indications in PD to guide clinical trials for homogeneous patient selection.

Cerebrospinal fluid (CSF) analysis provides a mechanism to detect and measure protein species related to the accumulation of these pathological proteins over time in living patients; cross-sectional work finds CSF measures of AD pathology associate with cognitive performance[3–6] and postmortem severity of AD co-pathology in PD[7]. Moreover, CSF tau and aSyn levels are highly correlated and, on average, lower in PD compared to controls[8, 9]; however, longitudinal AD CSF biomarker data in PD is rare[10–14] and detailed longitudinal modeling of progressive changes in values are lacking.

One obstacle to longitudinal CSF studies is inter- and intra-assay variation[15] which could reduce the sensitivity to detect changes between repeated measurements from an individual over time in longitudinal biomarker studies. The Roche Elecsys® analytical platform is fully-automated with high-reliability for measurement of AD CSF biomarkers[16–18] and was previously validated with a reference measurement procedure approved by the Joint Committee for Traceability in Laboratory Medicine for CSF $A\beta_{42}$[19]. PPMI[20] is a unique multicenter international observational study collecting long term annual detailed harmonized clinical measures and biomarkers in a large cohort of newly diagnosed drug-naïve PD. We previously found CSF measurements of tau and $A\beta_{42}$, as well as aSyn, related to cross-sectional and longitudinal clinical features in this cohort with follow-up up to one year[8, 9, 12, 21].

Using the rich PPMI dataset with standardized longitudinal data for up to three years and the Elecsys® high-precision analytical platform, we evaluated the baseline and longitudinal progression of AD CSF biomarkers in PD and tested the relationship of these with clinical features.

METHODS

Sample

The sample consisted of participants in two of the cohorts of the PPMI multicenter prospective longitudinal observational study: early PD, drug-naïve at baseline, and HC[20], with diagnostic criteria for enrollment as described previously[8, 9]. Those included for study (n=608) had at least one CSF sample at any timepoint available as of May 7th, 2018 (PD=416, HC=192). We did not include other PPMI cohort participants (symptomatic or asymptomatic individuals with PD-related genetic mutations, prodromal PD, or participants with parkinsonism but without evidence of dopaminergic deficit syndrome). CSF and clinical data were obtained from PPMI database for baseline, 6 months and annual follow up visits at years 1, 2 and 3. A subset of these participants were previously reported in a cross-sectional study of baseline CSF data (n=601)[8, 9] or longitudinal CSF with only 1-year follow up (n=285)[12] and using a different immunoassay platform (i.e. Innogenetics AlzBio3 Luminex platform).

All procedures were performed with prior approval from ethical standards committees at each participating institution and with informed consent from all study participants. The study is registered in clinicaltrials.gov as NCT01141023.

CSF Analysis

CSF collection, shipment and storage were performed using standard operating procedures at each institution as described in detail previously (please see biologics manual ppmi.info.org). CSF samples were shipped from the PPMI Biorepository Core laboratories to the University of Pennsylvania (Penn) Biomarker Research Laboratory for measurement of CSF amyloid-beta 1–42 ($A\beta_{42}$), total-tau (t-tau) and tau phosphorylated at threonine 181 position (p-tau) using Elecsys® electrochemiluminescence immunoassays on the cobas e 601 analysis platform (Roche Diagnostics) as described[16, 18]. The analytical measurement range for the $A\beta_{42}$ assay was 200 to 1700 pg/mL, the t-tau assay was 80 to 1300 pg/mL and the p-tau181 assay: 8 to 120 pg/mL. Roche extrapolated values above the upper technical limit from the calibration curve, 1700 pg/ml, in 96 measurements of $A\beta_{42}$. Performance of this platform has been previously reported with intra- and inter-CV% <5%[17–19]. CSF total alpha-synuclein (aSyn) data from baseline visits were obtained from PPMI database and measured by BioLegend (San Diego, CA) using a commercially available sandwich immunoassay, as previously described[8, 9, 12].

Clinical Data

Clinical data for each visit was obtained from the PPMI database as above and described in detail previously[22]. Variables included for analysis were demographics (age at baseline, age at symptoms onset, disease duration at visit, years of education and sex) and cognitive and motor testing scores. We chose continuous measures of cognitive functioning in several domains including: global functioning (Montreal Cognitive Assessment; MoCA), episodic memory (Hopkins Verbal Learning Test discrimination recognition score; HVLT), visuospatial functioning (Benton judgement of line orientation score; JOLO), language (semantic fluency; SF) and executive functioning (letter number sequencing; LNS). For motor functioning we used the Movement Disorders Society modified Unified Parkinson's disease rating scale (MDS-UPDRS) part III total score and motor sub-scores for tremor and postural instability (PIGD), as previously defined[9], as continuous variables. We also included the total score for the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) to capture non-motor/cognitive autonomic aspects of PD.

Genetic Data

Blood samples were analyzed for *apolipoprotein ε* (APOE) genotype at the PPMI genetics core as described[8] and coded for analyses as the presence or absences of one or more ε4 alleles (i.e. dominant model).

Statistical Analyses

Data used in study were downloaded from PPMI database on May 7th 2018 and analyzed at the University of Iowa using SAS 9.4 Software (SAS Institute, Cary, NC) or at Penn using SPSS version 24.0 (IBM, Chicago, IL). We used a significance threshold of $p<0.05$ due to

the hypothesis-driven approach for CSF-clinical correlations (please see results section for specifics).

Continuous demographic, clinical and biomarker data were compared between groups using Student's t-test or Wilcoxon rank-sum test, as appropriate, and nominal variables compared with a chi-square or Fisher's exact test. For non-parametric comparisons we calculated effect size $r=z/\sqrt{(N)}$, where N is the total sample size[23].

To test for associations of needle type used in CSF collection, we used univariate comparisons for measures of each analyte using the Kruskal-Wallis test within PD subjects. CSF needle was grouped by type coded in database: Quincke, Sprotte, or "other".

Correlations between CSF biomarkers were computed using Spearman rank correlation and 95% confidence intervals (CI) obtained based on Fisher's z transformation. To test biological associations of CSF biomarkers, we performed univariate subgroup analysis within PD and HC groups comparing patients with one or more copies of APOE ε4 allele compared to those without.

To characterize the AD CSF profile of PD and HC we applied a cut-point for amyloid-positivity established in AD[16]. To mitigate differences in pre-analytical factors between PPMI and AD cohorts that influence CSF $A\beta_{42}$ levels[24], we used the transformation formula from Shaw et al[25] to convert Elecsys values to AlzBio3 equivalents [$x= (\text{CSF } A\beta_{42} +251.55)/3.74$] and applied the established cut-point of <250 pg/ml of AlzBio3 equivalent values[16] to designate amyloid-positivity. A chi-square test was used to analyze proportional differences in amyloid-positivity among PD and HC at baseline. Within PD and HC, we compared demographics and CSF biomarker values between amyloid-positive and negative groups using univariate statistics.

For longitudinal analyses we focused on core AD CSF biomarkers (Aβ42, t-tau, and p-tau), rather than ratios of these analytes, to more directly test biomarker associations. To assess the difference in mean change from baseline for each AD CSF analyte between the PD and control groups, we used rank-based linear mixed models (LMM) with adjustment for age, sex and the baseline value of the CSF outcome. Akaike information criterion (AIC) was used in the determination to adjust for APOE and the model fit of including an interaction between time and group (i.e PD vs HC). We report the p-value from the rank-based LMM and mean estimates from a model based on the untransformed values for ease of interpretation. The model-based mean estimates of the change in CSF within PD and HC and their differences adjust for group specific differences in the baseline covariates (age, sex, baseline CSF, and APOE (if applicable)).

To test the associations between baseline CSF analyte levels and decline on clinical measures in PD, we used LMM or rank-based LMM with separate models for each baseline CSF measure as predictors for the dependent variable of change in each clinical measure (MoCA, HTLV, JLO, SF, LNS, UPDRS III total, tremor UPDRS subscore, PIGD UPDRS subscore and SCOPA-AUT) from baseline in PD subjects. All models adjusted for baseline age, gender, disease duration, and the baseline value of the clinical measure. AIC was used in the determination to adjust for APOE in the final models and to compare the model fit of

including an interaction between time and baseline CSF. If AIC indicated the interaction did not provide better fit, the interaction term was removed. Using this approach, we found the optimal model structure for MoCA, LNS, UPDRS III and SCOPA-AUT was a linear time model with a random intercept and slope and an unstructured covariance structure. The optimal model for SF was a linear time model with a random intercept and an unstructured covariance structure. A non-linear time model had optimal fit for JLO. The final models for the clinical outcomes in LNS adjusted for APOE along with the MoCA models for $A\beta_{42}$ and aSyn. Rank-based LMM were fit for Tremor, PIGD, and HVLT. We report the p-value from the rank-based LMM and effect estimates from a model based on the untransformed values for ease of interpretation.

RESULTS

Patient Demographics and Baseline Characteristics

PD and HC patient demographics are listed in Table 1. Similar to previous reports of this cohort at baseline[8, 9], PD and HC groups did not differ in age, sex or *APOE* allele status.

Cross-Sectional CSF Analysis

First, to test for pre-analytical factors that could influence CSF measurements on this platform, we performed univariate comparisons of needle type used in CSF collection cross-sectional data at each time point for CSF $A\beta_{42}$, t-tau and p-tau. We did not find any association of needle type with biomarker values (data not shown) and needle-type did not have a significant effect on any of our subsequent CSF outcome models below.

Baseline levels of CSF $A\beta_{42}$, t-tau, p-tau, aSyn and the ratio of p-tau/t-tau were lower in PD than HC (effect size=0.09–0.17, p<0.03–0.0001), while the ratios of t-tau/$A\beta_{42}$, p-tau/$A\beta_{42}$, t-tau/aSyn, p-tau/aSyn, $A\beta_{42}$/aSyn were similar between groups (Figure 1). These group-level differences were similar across timepoints (Table 2); however, despite group-wise differences in these CSF biomarkers, there was individual-patient overlap in values between groups (Figure 1).

Next, to test the association of AD CSF biomarkers with a known genetic marker of AD pathology[26], we compared both PD and HC individuals with one or more copies of APOE ε4 genotype to those with no copies of APOE ε4 at baseline and found lower CSF $A\beta_{42}$ in APOE ε4 carriers for both PD and HC (effect size=0.26–0.31, p<0.0001), while there was no difference between APOE genotype groups within PD or HC for t-tau or p-tau (Table 3). Interestingly, there was also lower baseline CSF aSyn in PD APOE ε4 carriers than non-carriers (effect size= 0.13, p=0.01), while CSF aSyn was similar between HC APOE groups (Table 3).

We found a moderate to strong correlation among AD CSF biomarkers ($A\beta_{42}$ vs t-tau Rho=0.59, 95%CI (0.53–0.64), p<0.0001, n=583; $A\beta_{42}$ vs p-tau Rho=0.51, 95%CI (0.45–0.57), p<0.0001, n=548; t-tau vs p-tau Rho=0.97, 95%CI (0.97–0.98), p<0.0001, n=555) and with AD CSF biomarkers and CSF aSyn ($A\beta_{42}$ vs aSyn Rho=0.60, 95%CI (0.55–0.65), p<0.0001, n=597; t-tau vs aSyn Rho=0.80, 95%CI (0.77–0.83), p<0.0001, n=589; p-tau vs

aSyn Rho=0.80, 95%CI (0.77–0.83), p<0.0001, n=554) in the total cohort at baseline (Figure 2).

Finally, we examined cross-sectional profiles of patients with presumed amyloid-positivity in PD and HC at baseline using an established cut-point in AD[16]. We found at baseline, relative equal frequencies of pathologically low CSF $A\beta_{42}$ indicative of amyloidosis (+A) in PD (31.5%) and HC (27.7%) (Table 4) with no differences in demographics between PD+A and PD with normal CSF $A\beta_{42}$ (-A) or HC+A and HC-A; however, there were lower CSF t-tau, p-tau and aSyn levels in PD+A vs PD-A (effect size=0.29–0.45, p<0.0001). In contrast, there was no difference in CSF p-tau between HC+A and HC-A, but CSF p-tau was lower in PD+A than HC+A (effect size= 0.19, p<0.03), suggesting a divergent interaction between AD CSF biomarkers in PD compared to controls (Table 4).

Longitudinal Change in AD CSF Biomarkers

To further test the profile of AD CSF biomarkers longitudinally in PD vs HC, we performed linear-mixed model analysis to test the mean change from baseline at each time point between PD and HC. We did not find an interaction between group and time, suggesting the difference in change between PD and HC was largely constant over the three-year period (Figure 3). PD had greater decline in all three biomarkers over time; we found greater reduction in CSF $A\beta_{42}$ (mean difference= −41.83 pg/ml, SE=18.94, p=0.03) and p-tau (mean difference= −0.38 pg/ml, SE=0.22, p=0.03), in PD compared to HC with a trend for CSF t-tau (mean difference= −3.7 pg/ml, SE=2.7, p=0.07) (Table 5). Examination of estimates of mean change at each time point in our models finds an increasingly negative mean change in CSF $A\beta_{42}$ in PD compared to HC, where there is mild decline only at year three, and in PD more modest mean increases in CSF t-tau and p-tau seen only at year three compared to more consistent increases over time in HC (Table 5).

Prediction of Longitudinal Cognitive, Motor and Autonomic Decline using Baseline AD CSF Biomarkers

We performed exploratory analyses based on previous postmortem[27–30] and biomarker work[3–5] to test predictive value of AD CSF biomarkers in PD. We hypothesized that AD CSF biomarkers would relate to overall cognitive decline, and more specifically in temporal-lobe mediated episodic memory and semantic fluency tasks. Moreover, we expected CSF aSyn would relate to decline on traditional-reported cognitive deficits in early PD[22, 31, 32]: spatial and executive/attention/working memory tasks. Further, we hypothesized CSF aSyn would relate to progression of classic PD features of motor impairment and autonomic instability. Finally, based on recent postmortem work[27], we expected greater increase in motor postural instability to associate with lower CSF AB_{42}.

We found greater baseline p-tau (β= −0.47 points per 10 pg/mL, 95%CI: (−0.91- −0.03), p<0.05) and lower CSF $A\beta_{42}$ (Month 24 β=0.06 points per 100 pg/mL, 95%CI: (0.01–0.10), p=0.02; Month 36 β=0.09 points per 100 pg/mL, 95%CI: (0.03–0.15), p<0.01) predicted greater decline in global cognition (i.e. MOCA). We also found that both lower CSF baseline $A\beta_{42}$ (β=0.04 points per 100 pg/mL, 95%CI: (0.0003–0.09), p<0.05) and aSyn (β=0.03 points per 100 pg/mL, 95%CI: (0.003–0.06), p=0.03) predicted greater decline in working

memory (i.e. LNS). There was a non-significant trend for greater baseline CSF t-tau to be associated with longitudinal decline on semantic fluency (β= −0.57 points per 100 pg/mL, 95%CI: (−1.17– 0.03), p=0.06).

We found both lower baseline CSF $A\beta_{42}$ and aSyn were associated with increased postural instability subscores (aSyn β= −0.004 points per 100 pg/mL, 95%CI: (−0.008- −0.0007), p<0.02; $A\beta_{42}$ β=−0.007 points per 100 pg/mL, 95%CI: (−0.01- −0.001), p=0.04) and total UPDRS III motor scores (aSyn β=−0.10 points per 100 pg/mL, 95% CI: (−0.19- −0.003), p=0.04; $A\beta_{42}$ β=−0.16 points per 100 pg/mL, 95% CI: (−0.30- −0.01), p=0.03). Finally, lower baseline CSF $A\beta_{42}$ was also associated with an increase in autonomic symptoms on SCOPA-AUT (β=−0.12 points per 100 pg/mL, 95% CI: (−0.21- −0.02), p=0.02). We did not find other associations with baseline CSF biomarkers and longitudinal clinical measures (data not shown).

DISCUSSION

In this large-scale longitudinal study of well-characterized PD patients over a three-year period using a precise analytical platform (the Roche Elecsys® system) to measure AD CSF biomarker analytes we have several important findings. First, we find lower overall AD CSF biomarker values in PD vs HC (Figure 1, Table 2), with a moderate-to-strong correlation between markers in both PD and HC (Figure 2). 31.5% of PD had pathologically low CSF $A\beta_{42}$ at baseline with relatively low CSF p-tau compared to HC with pathological CSF $A\beta_{42}$ (Table 4). Moreover, we found modest but novel measurable group-level changes in AD CSF biomarkers over time in PD that were distinct from HC, with greater overall decline in CSF $A\beta_{42}$ and p-tau in PD (Figure 3, Table 5). Finally, we find preliminary evidence for predictive value of CSF $A\beta_{42}$ for global and domain-specific cognitive decline, motor and autonomic function in PD. These data have important implications for the interpretation of these emerging CSF biomarkers in PD.

Our group-wise comparisons at baseline (Figure 1, Table 2) using the high-precision immunoassay replicated previous findings of lower CSF levels of t-tau and p-tau on average in PD than HC and a strong correlation with CSF aSyn (Rho=0.8–0.9) (Figure 2)[8–10]. Similar to another study of early PD[5], we found lower CSF $A\beta_{42}$ in PD compared to HC and moderate correlations of CSF $A\beta_{42}$ with CSF t-tau, p-tau and aSyn in both PD and HC (Figure 2). Moreover, low baseline CSF $A\beta_{42}$ in this PD cohort was overall associated with lower baseline levels of CSF t-tau and p-tau, rather than higher levels of CSF tau as in preclinical and clinical AD cohorts[16]. Indeed, in our unique analysis applying an established AD cut point for CSF $A\beta_{42}$, we found approximately one-third of PD had pathologically-low CSF $A\beta_{42}$ (PD+A). Moreover, these patients had, on average, lower p-tau levels compared to HC with pathologically-low $A\beta_{42}$ (HC+A; Table 4), suggesting the profiles of CSF $A\beta_{42}$ and p-tau in PD may diverge from aging and AD. Interestingly, HC+A had lower CSF t-tau and aSyn compared to HC with normal CSF $A\beta_{42m}$ (HC-A, Table 4) which is opposite than expected; however, there was heterogeneity in values with higher overall range in these analytes than seen in PD. Our observed frequency of 31% of early PD with positive AD CSF biomarker profile is similar to autopsy data in end-stage PD[1], but lower than a previous study using a CSF p-tau/$A\beta_{42}$ ratio to designate AD positive profile[10]. Our findings

of low CSF p-tau in PD at baseline and follow-up suggest that a CSF p-tau cut-point established in AD cohorts may underestimate the frequency of AD co-pathology in PD. This is important to consider as biomarker classification strategies are being employed in AD and related neurodegenerative conditions[33].

To further clarify the biological context of our findings, we tested the association of CSF $A\beta_{42}$ with APOE ε4 genotype, and similar to previous studies[8, 10, 11], we found lower levels in APOE ε4 carriers vs non-carries for both PD and HC groups (Table 3). These data suggest our measurements are related, at least in part, to amyloid-beta pathophysiology in PD. Interestingly, we also found lower CSF aSyn in APOE ε4 carriers compared to non-carriers for PD but not HC; previous autopsy work finds an association of APOE ε4 with pure aSyn neuropathology[34] suggesting shared genetic risk for amyloidosis and aSyn aggregation that may be reflected in our CSF findings here. Interestingly, our clinical correlations, while preliminary, found similar associations of both CSF $A\beta_{42}$ and aSyn with core clinical features of PD (see below), further suggesting these biomarkers may in part reflect similar underlying pathophysiological processes in PD.

Longitudinal analysis of CSF biomarkers in PD are rare[10, 12, 14] with conflicting results. One study that included 30 sporadic PD patients found lower CSF $A\beta_{42,}$ t-tau and p-tau in PD compared to controls at baseline and 24-month follow-up[13]. Whereas in 62 PD patients of the BioFINDER study, on average there was an increase in CSF t-tau and p-tau at 24 months that was most pronounced in PD patients with longer disease duration[14]. In a large-scale prospective PD cohort with follow-up up to 8 years there was lower CSF $A\beta_{42}$ in PD patients who developed cognitive impairment with more stable levels in PD without cognitive impairment[11], but neither this study, the similarly-sized DATATOP study[10], or other studies above modeled longitudinal change of CSF biomarkers over time.

Here, with the first automated high-precision measurements in PD and statistical modelling to account for demographic factors in the longitudinal change in biomarkers, we find modest but measurable group-wise changes in AD CSF biomarkers over a three-year period (Table 5, Figure 3). Importantly we find that the longitudinal profile in PD diverges from HC with greater overall decrease in CSF $A\beta_{42}$ and lower overall increases in CSF t-tau and p-tau by year three. We previously reported a slight increase in CSF $A\beta_{42}$ and CSF p-tau in the PPMI PD cohort at year one using the AlzBio3 assay and shorter follow-up[12]. There are several possibilities for discrepancies in the previous literature, including the size and demographic makeup of the patient population (e.g. stage/severity of disease), statistical approach and increased precision of the automated analytical platform in this study[19]. Moreover, there was large individual patient variability in this study (Figure 3) and our statistical modelling helped account for demographic and *APOE* status which could influence longitudinal measures of CSF analytes and obscure group-wise differences using traditional cross-sectional analyses used in previous work. Indeed, our observations in HC here are congruent with previous longitudinal CSF data in cognitively normal aged patients with mild decreases in CSF $A\beta_{42}$ and increases in CSF t-tau and p-tau[35, 36].

It is interesting to hypothesize the mechanism for our observations of decline in CSF $A\beta_{42}$ in PD; as aforementioned, while low CSF $A\beta_{42}$ has been linked to amyloid-beta

pathophysiology in PD[7, 37], low CSF $A\beta_{42}$ may have independent associations with aSyn pathology[7] and perhaps in some PD patients low CSF $A\beta_{42}$ is reflective of mechanisms related to underlying aSyn pathology prior to, or in absence of, the accumulation of cerebral amyloidosis. We also found CSF t-tau and p-tau had divergent longitudinal profiles from HC, with minimal change until years 2–3, where there was mild overall increase in levels compared to the greater mean increases seen in HC (Table 5). Thus, the longitudinal profile of increasing CSF t-tau and p-tau with age may be partially suppressed in the context of PD. Other longitudinal studies with more advanced PD suggest highly correlated levels CSF tau and aSyn levels may eventually increase over time in more advanced disease[14] and cross-sectional work finds greater CSF t-tau and p-tau levels in PDD compared to PD without dementia[38]. Moreover, both CSF aSyn and tau levels are elevated in AD[39], suggesting increasing neurodegeneration may lead to increased CSF tau and aSyn. Thus, future work with molecular imaging and autopsy data are needed to establish CSF cut-points to accurately detect AD co-pathology in PD for prognosis and to elucidate the underlying pathophysiological changes contributing to patterns observed here.

Our longitudinal clinical correlation analyses provide further insight into the interpretation of these CSF markers in PD. While there are currently relative mild levels of overall cognitive impairment in the PPMI PD cohort even after 5 years[21, 40], we found evidence for lower baseline CSF $A\beta_{42}$ to predict global cognitive decline (i.e. change in MoCA score) in PD, similar to previous work[3, 5, 11, 13, 21, 41–45]. Moreover, we also found more modest associations of greater baseline CSF p-tau to predict decline in MoCA score in our PD cohort, similar to one study[44] but not others[13, 43]. One possible interpretation is that despite the overall trend of declining CSF p-tau in the PD group, there is heterogeneity and some PD patients at risk for cognitive impairment have an early increase in p-tau levels. Future work with longer follow-up can elucidate potential biomarker-defined subgroups of PD. Nonetheless, these data suggest that baseline AD CSF profiles may have prognostic value for overall incipient cognitive decline in PD.

Cognitive impairment in PD is heterogeneous and although attention, working memory, executive abilities and visuospatial dysfunction are considered to be the core clinical features in the majority of initial PD cognitive deficits[22, 31, 32], episodic memory loss and language dysfunction are not uncommon and previously linked to AD pathology[28–30]. Thus, we hypothesized domain-specific associations of AD CSF biomarkers for episodic memory and semantic fluency but surprisingly did not find an association. Instead, we found both lower CSF $A\beta_{42}$ and CSF aSyn had predictive value of cognitive decline in working memory (i.e. a core cognitive feature of PD) and decline in motor UPDRS III total and PIGD sub-scores. Moreover, CSF $A\beta_{42}$ alone predicted worsening of autonomic symptoms in PD. One study of early PD similarly found lower CSF $A\beta_{42}$ related to postural instability scores[46] and postmortem amyloid-pathology has been linked to postural instability in PD[27]; however our data also conflicts with some previous work that found associations of baseline AD CSF biomarkers with measures of memory impairment[5] and findings of greater baseline CSF aSyn associated with cognitive and motor decline in PD[42, 47]. Moreover, another study of early PD did not find an association of CSF aSyn with cognitive or motor decline[48] while, p-tau/t-tau and p-tau/$A\beta_{42}$ ratios have been linked to motor decline in PD in one large-scale study[10]. Thus, there is a complex literature on baseline CSF biomarker prediction of

progression in PD with varying methodologies and patient compositions which could contribute to these discrepancies, necessitating replication with follow-up capturing end-stage disease to fully discern predictive values of CSF biomarkers in PD. Here, the effect sizes of these changes were relatively small and statistical associations marginal so these findings remain preliminary in this early stage of PD; however the overall pattern of CSF $A\beta_{42}$ clinical associations with core features of PD reinforce the possibility that this analyte may reflect biological processes integral to the pathophysiology of PD.

There are several limitations to acknowledge in this study. First, while this cohort represents a unique large-scale international coordinated multicenter effort to collect standardized longitudinal assessments, findings in this dataset from a research setting require replication in independent population-based cohorts to generalize findings. The Roche Elecsys® platform has advantages of high precision (%CV values<5%), linearity of dynamic range of measurements[16–19] and standard operating procedures were used for harmonized methods of CSF collection across PPMI sites; we examined the effect of needle-type used during the LP procedure and found no significant association of needle-type with any of our AD CSF biomarkers, similar to other recent work in AD[49], providing further critical data to optimize large-scale multicenter biomarker efforts needed to establish CSF biomarkers for use in clinical practice. While our predictive models were robust, the magnitude of change in our clinical and biomarker values were relatively modest, likely due to the early stage of disease and relative short duration of follow-up for longitudinal biomarker values that may take decades to show progression[50]. Finally, future work relating CSF biomarker profiles across the full natural history of PD to *in vivo* measures of pathology and autopsy data is needed to fully resolve the biological context of these analytes in PD. Nonetheless our unique large-scale longitudinal data suggest a distinct CSF AD biomarker profile in early PD with relatively greater decline in CSF $A\beta_{42}$ and p-tau. Moreover, we find preliminary evidence of early predictive value of subtle changes in CSF biomarkers for cognition, motor and autonomic function in PD. Further follow-up of the PPMI cohort and other ongoing longitudinal PD studies[5, 11, 14, 45] will be needed to determine predictive value for clinically relevant changes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential Conflicts of Interest

Dr. Mollenhauer has received honoraria for consultancy from Roche, Biogen, UCB and Sun Pharma Advanced research Company. Dr. Kieburtz reports other from Clintrex Research Corp, other from Hoover Brown LLC, outside the submitted work; Dr. Galasko reports personal fees from Biogen, Inc, personal fees from vTv Pharmaceuticals, Inc, personal fees from Fujirebio, Inc, personal fees from Cognition therapeutics, outside the submitted work; .Dr. Simuni reports grants from Biogen, Roche, Neuroderm, Sanofi, Sun Pharma, Abbvie, IMPAX, Prevail, other from Acadia, Abbvie, Accorda , Adamas, Allergan, Amneal, Aptinyx, Denali, General Electric (GE) , Kyowa, Neuroderm, Neurocrine , Sanofi, Sinopia, Sunovion, Roche, Takeda, Voyager, US World Meds, during the conduct of the study; Dr. Tanner reports grants from Gateway LLC, grants from Roche/Genentech, grants and personal fees from Biogen Idec, personal fees from Acorda, personal fees from Adamas Therapeutics, personal fees from Amneal, personal fees from CNS Ratings, personal fees from Grey Matter LLC, personal fees from Northwestern University, personal fees from Partners, Harvard U, outside the submitted work; .Dr. Marek reports consulting from Michael J Fox, GE Heathcare, Takeda, Lundbeck, Neuron23, Roche, Neuroderm, o Invicro, outside the submitted work; PPMI is supported in part by Roche who manufacture the Elecsys® assays used in the study.

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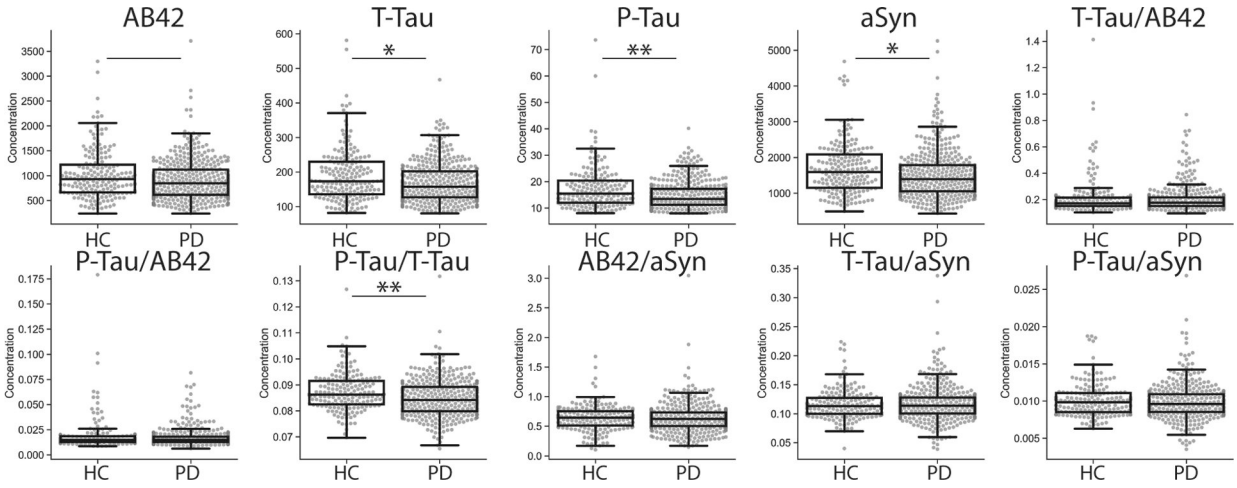

Figure 1. Group-wise comparison of baseline CSF biomarkers in PD and HC.

Solid line represents group-wise difference between PD and HC $p<0.05$, solid line plus single asterisk $p<0.01$ and solid line plus double-asterisk $p<0.001$.

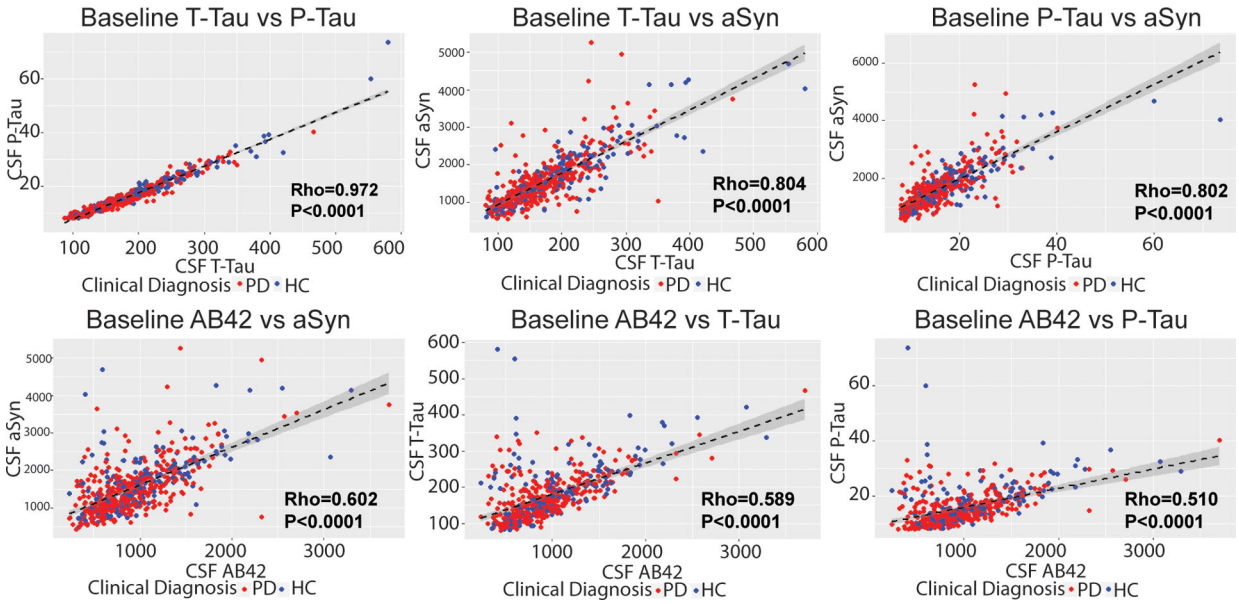

Figure 2. Baseline correlation of CSF biomarkers in PD and HC.

Scatterplots depict individual patient datapoints for CSF values at baseline. Dashed-line represents fitted line with 95% confidence interval. Red=PD, Blue=HC.

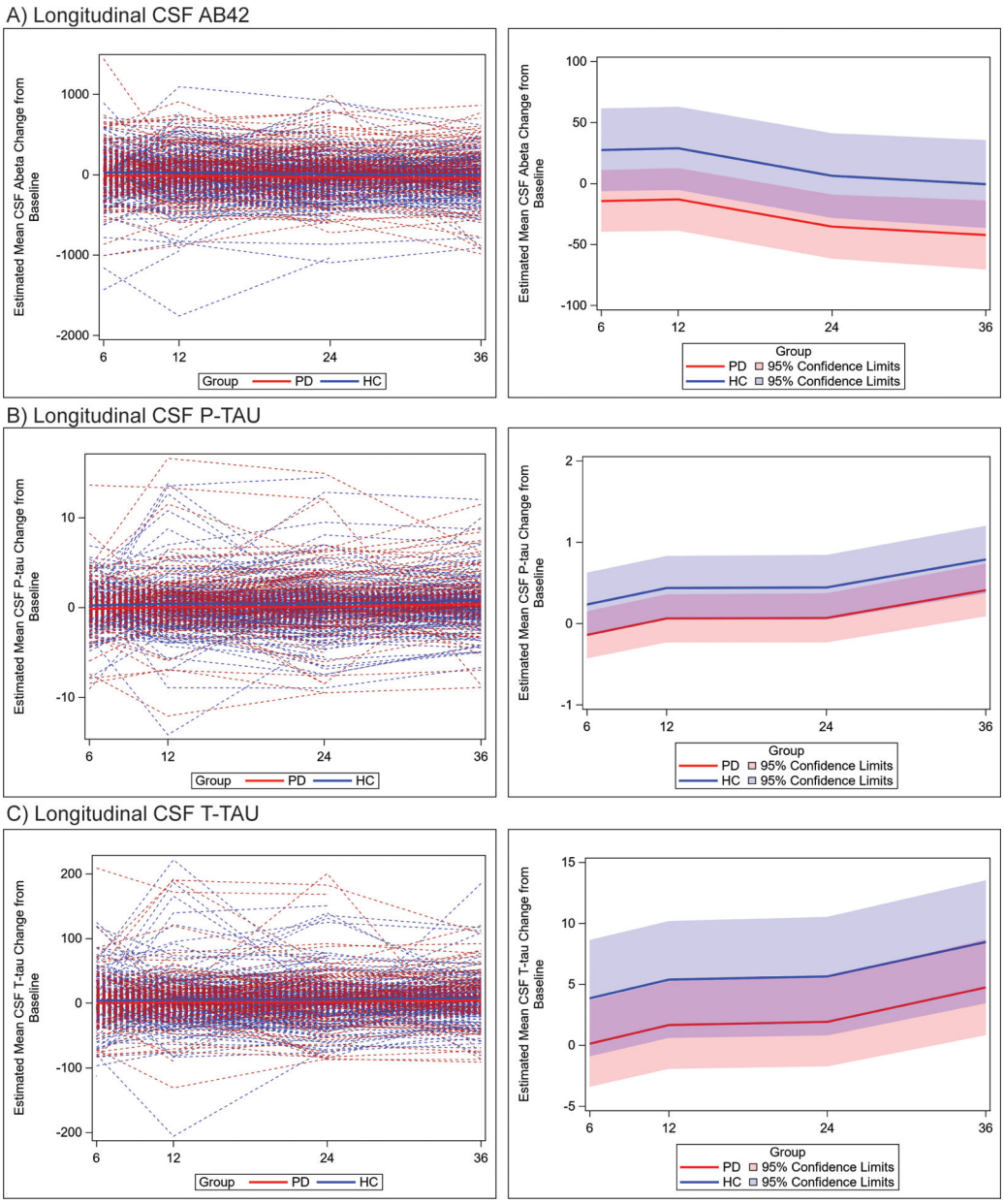

Figure 3. Individual patient data for median change in AD CSF biomarker measurements at each time point.

Spaghetti plot depicts individual-patient trajectories (left panels) and trend lines (right panels) depict mean values for PD (red) and HC (blue) and 95% CI for mean change in biomarker value at each time point using LMM adjusted for age, sex, and the baseline value of the CSF outcome for mean change in measurements for CSF Aβ42 (A) t-tau (B) and p-tau (C) at 6 months, 12 months, 24 months and 36-month time points. Across all time points we found a greater reduction in CSF Aβ42 (mean difference −41.83 pg/ml, SE=18.94, p=0.03) and p-tau (mean difference=−0.38 pg/ml, SE=0.22, p=0.03), in PD compared to HC with a non-significant trend for CSF t-tau (mean difference=−3.7 pg/ml, SE=2.7, p=0.07).

Table 1.

Patient and Control Demographics and Baseline Characteristics

Variables		PD N=416	HC N=192	P-value
DEMOGRAPHIC	Age (y)	61.7 (9.6)	60.8 (11.3)	0.3
	Sex	Male=272 (65.4%) Female=144 (34.6%)	Male=123 (64.0%) Female =69 (35.9%)	0.8
	Education (y)	15.5 (3.0)	16.0 (2.9)	0.06
	APOE ε4 Status	0 alleles= 277 (73.3%) 1 allele= 92 (24.3%) 2 alleles= 9 (2.4%) Missing data=38	0 alleles= 129 (73.7%) 1 allele= 42 (24.0%) 2 alleles= 4 (2.3%) Missing data=17	>0.99
	Age at Onset (y)	59.7 (9.9)	NA	-
	Disease Duration (mo)	6.7 (6.5)	NA	-
MOTOR	UPDRS III Tremor	0.5 (0.3) N=415 Missing data=1	0.03 (0.08) N=191 Missing data=1	<0.0001
	UPDRS III PIGD	0.23 (0.22) N=415 Missing data=1	0.02 (0.09) N=191 Missing data=1	<0.0001
COGNITIVE	MOCA	27.1 (2.3) N=413 Missing data=3	28.2 (1.1) N=192	<0.0001
	HVLT	10 (−4,12) N=414 Missing data=2	11 (−4, 12) N=192	<0.001
	SFT	48.8 (11.6) N=415 Missing data=1	51.9 (11.3) N=192	<0.01
	JLO	13 (5,15) N=415 Missing data=1	14 (4, 15) N=192	0.06
	LNS	10.6 (2.6) N=415 Missing data=1	10.9 (2.6) N=192	0.1

Data listed= mean (SD) for normally distributed variables or median (range) for non-normally distributed variables and frequency (%) for categorical variables. Missing Data noted in each cell where applicable.

Abbreviations: PD=Parkinson's disease, HC=healthy controls, y= years, mo=months, APOE=apolipoprotein E, UPDRS= Unified Parkinson's Disease Rating Scale, Tremor=Tremor sub score of UPDRS, PIGD= Postural instability and gait disturbance sub score of UPDRS, MOCA= Montreal Cognitive Assessment, HVLT= Hopkins Verbal Learning Test Discrimination Recognition Score , SFT= semantic fluency total score, JLO= Benton judgement of line orientation score, LNS= Letter-number sequencing score.

Table 2.

Cross-Sectional Cerebrospinal Fluid Biomarker Data

Analyte	Visit	PD (N=416)	HC (N=192)	Effect Size r	P-value
Aβ42	Baseline	846.15 (238.80 – 3707.00) Missing data=6	926.45 (239.10 – 3297.00) Missing data=4	0.09	0.02
	6 Months	849.70 (267.30 – 2888.00) Missing data=77	938.90 (372.90 – 3272.00) Missing data=35	0.14	<0.002
	Year 1	821.30 (249.50 – 2480.00) Missing data=90	1019.50 (312.00 –2678.00) Missing data=40	0.18	<0.0001
	Year 2	849.75 (260.30 – 3000.00) Missing data=112	955.75 (248.60 – 3551.00) Missing data=56	0.13	<0.01
	Year 3	855.25 (240.80 – 2396.00) Missing data=194	954.30 (282.00 – 2842.00) Missing data=79	0.12	0.03
t-tau	Baseline	157.70 (80.93 – 467.00) Missing data=13	173.50 (81.96 – 580.80) Missing data=5	0.12	<0.01
	6 Months	153.60 (80.64 – 387.50) Missing data=81	179.60 (82.64 – 551.50) Missing data=37	0.19	<0.0001
	Year 1	155.60 (82.24 – 388.70) Missing data=94	178.80 (82.36 – 600.10) Missing data=40	0.18	<0.0001
	Year 2	156.35 (80.88 – 463.60) Missing data=110	178.80 (85.92 – 619.70) Missing data=60	0.18	<0.001
	Year 3	160.45 (80.98 – 444.50) Missing data=190	173.60 (83.48 – 569.40) Missing data=79	0.16	<0.01
p-tau	Baseline	13.40 (8.01 – 40.13) Missing data=37	15.44 (8.08 – 73.61) Missing data=16	0.17	0.0001
	6 Months	13.34 (8.00 – 36.94) Missing data=106	15.69 (8.53 – 69.10) Missing data=42	0.20	<0.0001
	Year 1	13.41 (8.05 – 34.28) Missing data=124	15.87 (8.30 – 80.08) Missing data=48	0.21	<0.0001
	Year 2	13.39 (8.13 – 43.69) Missing data=136	15.59 (8.00 – 80.54) Missing data=66	0.21	<0.0001
	Year 3	13.31 (8.03 – 42.87) Missing data=205	15.31 (8.05 – 78.34) Missing data=90	0.22	0.0001
aSyn	Baseline	1390.50 (432.40–5256.90) Missing data=2	1593.50 (488.60–4683.10) Missing data=2	0.13	<0.002
t-tau/Aβ42	Baseline	0.18 (0.10 – 0.84) Missing data=18	0.17 (0.10 – 1.41) Missing data=7	0.02	0.5
p-tau/Aβ42	Baseline	0.01 (0.01 – 0.08) Missing data=42	0.01 (0.01 – 0.18) Missing data=18	0.01	0.8
p-tau/t-tau	Baseline	0.08 (0.07 – 0.13) Missing data=37	0.09 (0.07 – 0.13) Missing data=16	0.16	<0.001
Aβ42/aSyn	Baseline	0.63 (0.15 – 3.04) Missing data=7	0.65 (0.10 – 1.68) Missing data=4	0.02	0.7
t-tau/aSyn	Baseline	0.11 (0.04 – 0.34) Missing data=14	0.11 (0.04 – 0.22) Missing data=5	0.02	0.5
p-tau/aSyn	Baseline	0.01 (0.00 – 0.03) Missing data=38	0.01 (0.01 – 0.02) Missing data=16	0.05	0.3

Data listed= median (range). Missing Data noted in each cell where applicable.

Abbreviations: PD=Parkinson's disease, HC=healthy controls, Aβ42= Cerebrospinal fluid amyloid-beta 1–42, t-tau= cerebrospinal fluid total tau, p-tau= cerebrospinal fluid phosphorylated tau at threonine 181, aSyn= cerebrospinal fluid total alpha-synuclein.

Table 3.

Baseline CSF Data by *APOE* Genotype

CSF Analyte	PD				HC			
	APOE 4+ N=101	APOE 4− N=277	Effect Size r	p	APOE 4+ N=46	APOE 4− N=129	Effect Size r	p
CSF Aβ42	697.1 (238.8 – 1795.0) Missing=1	912.8 (249.0 – 3707.0) Missing=4	0.26	<0.0001	673.1 (239.1 – 1890.0) Missing=1	994.8 (336.1 – 3297.0) Missing=3	0.31	<0.0001
CSF T-Tau	152.0 (85.0 – 349.8) Missing=5	159.9 (80.9 – 467.0) Missing=8	0.04	0.48	189.5 (93.3 – 554.5) Missing=2	168.6 (82.0 – 580.8) Missing=2	0.04	0.57
CSF P-Tau	13.3 (8.0 – 28.0) Missing=12	13.6 (8.0 – 40.1) Missing=22	0.03	0.56	17.0 (8.2 – 60.0) Missing=4	15.3 (8.1 – 73.6) Missing=10	0.05	0.52
CSF aSyn	1256.5 (432.4 – 3022.3)	1432.7 (472.0 – 5256.9) Missing=2	0.13	0.01	1522.0 (488.6 – 4683.1) Missing=1	1662.6 (600.7 – 4271.3) Missing=1	0.07	0.36

Data listed= median (range). Number of missing data points is noted in each cell. Abbreviations: PD=Parkinson's disease, HC=healthy controls, Aβ42= Cerebrospinal fluid amyloid-beta 1–42, t-tau= cerebrospinal fluid total tau, p-tau= cerebrospinal fluid phosphorylated tau at threonine 181, aSyn= cerebrospinal fluid total alpha-synuclein.

Table 4.

Baseline CSF AB Groups.

	PD-A	PD+A	HC-A	HC+A
N (% total)	281 (68.5%)	129 (31.5%)	136 (72.3%)	52 (27.7%)
Sex F (%F)	99 (35.2%)	41 (31.8%)	50 (36.8%)	18 (34.6%)
Age at CSF	61.47 (9.63)	62.2 (9.6)	60.7 (10.8)	61.0 (13.0)
Disease Duration	4.2 (0.4–35.8)	4.6 (0.7–34.7)	NA	NA
CSF T-Tau	169.50 (85.6–467.0)	124.1 *(80.9–339.2) Missing=12	183.0 (93.7–420.5)	126.8 (81.96–580.8) Missing=3
CSF P-Tau	14.04 (8.2–40.1) Missing=3	10.82 $^{*,\phi}$(8.0–32.8) Missing=33	15.6 (8.1–39.1) Missing=1	12.8 (8.2–73.6) Missing=13
CSF aSyn	1522.3 (606.1–5256.9) Missing=1	1026.6 *(432.4–3638.3)	1696.2 (733.8–4271.3)	1131.9 (488.6–4683.1)

Data listed= frequency (%) for categorical data, mean (standard deviation) for normally distributed data or median (range) for non-normally distributed data. Number of missing data points is noted in each cell. Abbreviations: PD-A=Parkinson's disease with normal CSF Aβ_{42} levels; PD +A= PD with pathologically low CSF Aβ_{42} levels, HC-A=healthy controls with normal CSF Aβ_{42} levels, HC+A=HC with pathologically low CSF Aβ_{42} levels, F= female, t-tau= cerebrospinal fluid total tau, p-tau= cerebrospinal fluid phosphorylated tau at threonine 181, aSyn= cerebrospinal fluid total alpha-synuclein.

*= p<0.0001 PD+A vs PD-A;

= p<0.0001 HC+A vs HC-A;

$^{\phi}$= p<0.03 PD+A vs HC+A.

Table 5.

Mean Estimates of Change in AD CSF Biomarkers in PD and Healthy Controls.

Variable	PD				HC			
	6 Months	1 Year	2 Years	3 Years	6 Months	1 Year	2 Years	3 Years
AB42								
Estimate (SE)	−14.29 (12.88)	−13.01 (13.08)	**−35.39 (13.36)***	**−42.27 (14.47)***	27.53 (17.28)	28.82 (17.37)	**6.44 (17.67)***	**−0.44 (18.38)***
(95% CI)	(−39.56, 10.97)	(−38.67, 12.65)	**(−61.60, −9.18)**	**(−70.65, −13.88)**	(−6.38, 61.45)	(−5.26, 62.89)	**(−28.23, 41.10)**	**(−36.50, 35.62)**
P-TAU								
Estimate (SE)	−0.14 (0.15)	0.06 (0.15)	**0.07 (0.15)***	**0.41 (0.16)***	0.24 (0.20)	0.44 (0.20)	**0.45 (0.20)***	**0.79 (0.21)***
(95% CI)	(−0.43, 0.15)	(−0.23, 0.36)	**(−0.23, 0.37)**	**(0.09, 0.74)**	(−0.15, 0.63)	(0.05, 0.83)	**(0.05, 0.84)**	**(0.37, 1.20)**
T-TAU								
Estimate (SE)	0.13 (1.81)	1.67 (1.83)	**1.93 (1.87)***	**4.75 (2.01)***	3.87 (2.43)	5.40 (2.44)	**5.66 (2.48)***	**8.49 (2.57)***
(95% CI)	(−3.41, 3.68)	(−1.93, 5.26)	**(−1.73, 5.59)**	**(0.81, 8.69)**	(−0.90, 8.63)	(0.61, 10.18)	**(0.80, 10.53)**	**(3.45, 13.52)**

Estimates based on the raw values (not the ranks) from models adjusting for age, sex and baseline CSF outcome value. AIC criteria determined APOE included in AB42 model.

* Denotes p<0.0001 for within-group comparison of estimates between time point and 6-month reference category.