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Cerebrospinal Fluid Biomarkers and Cognitive Performance in Non-Demented Patients with Parkinson's Disease

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Abstract

We tested the hypothesis that levels of CSF biomarkers associated with dementia and cognitive impairment are correlated with cognitive performance in non-demented Parkinson's disease (PD) patients. Twenty-two non-demented patients with PD underwent neuropsychological testing and lumbar puncture to collect CSF. We correlated performance scores on the Logical Memory (delayed), Category Fluency, Digit Symbol, and Trails B minus A with CSF concentrations of amyloid (A) β_{42} , total tau (t-tau), $A\beta_{42}/t\text{-tau}$, and Brain Derived Neurotrophic Factor (BDNF). We observed significant associations between performance on the Digit Symbol test and CSF levels of $A\beta_{42}$, $A\beta_{42}/t\text{-tau}$, and BDNF, and between performance on the Category Fluency (vegetable) and $A\beta_{42}/t\text{-tau}$. While several of these associations were attenuated by adjusting for age, our results suggest that it may be possible to use CSF biomarkers to characterize pathophysiologic processes underlying even mild cognitive deficits in non-demented PD patients.

Keywords

Parkinson disease; cognition; dementia; Alzheimer disease

Introduction

Cognitive impairment (CI) is an increasingly recognized non-motor complication of Parkinson's disease (PD). CI of sufficient severity to fulfill criteria for dementia occurs eventually in up to 80% of PD patients [1]. CI without dementia can occur quite early in PD,

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and frequently is present at the time of diagnosis [1]. Importantly, CI can dominate the clinical picture in mid to late stage disease and is a major source of morbidity for patients with PD [2].

The mechanisms underlying CI in PD are likely multifactorial and possibly convergent [3]. Recent neuropathologic studies have associated Lewy-related pathology in limbic and neocortical regions with CI, but some studies also have observed that a relatively large proportion of patients with PD and dementia (PD-D) have substantial changes of Alzheimer's disease [4–6]. Not surprisingly, vascular brain injury likely also contributes to CI in PD [3]. A limitation of autopsy-based investigations for a convergent phenotype is that variable and often lengthy amounts of time have passed between onset of cognitive impairment and pathologic examination.

A better understanding of the biologic processes contributing to CI in PD is particularly important as new disease-modifying treatments are developed. One method to investigate this issue early in the course of PD is through biomarkers. CSF biomarkers have proven to be valuable in Alzheimer's disease where reduction in A β ₄₂ levels and elevated tau and phosphorylated tau have been consistently demonstrated [7]. In fact, it appears that altered concentrations of these biomarkers, especially the ratio of A β ₄₂ and tau levels [8–10], can predict normal individuals at increased risk for progression to CI [7]. As yet, validated biomarkers for CI in PD have not been described, although emerging data suggest that decreased CSF A β ₄₂ without increased CSF tau concentrations may be associated with CI in PD [11], and other initial data suggest that CSF Brain Derived Neurotrophic Factor (BDNF) might have utility in the diagnosis of PD [12].

In this study we examined a group of non-demented PD patients who underwent detailed neuropsychological testing and lumbar puncture. We tested the hypothesis that, even in this non-demented group of PD patients, we would observe a relationship between cognitive performance and a subset of CSF biomarkers linked to CI in AD or PD.

Methods

Subjects were recruited through the Pacific Northwest Udall Center and University of Washington Alzheimer's Disease Research Center. The Human Subject Institutional Review Boards of the VA Puget Sound Health Care System and the University of Washington approved this study. All individuals provided informed consent and underwent evaluation that consisted of medical history, physical and neurologic examinations, laboratory tests, and neuropsychological assessment. Laboratory evaluation included complete blood count (serum electrolytes, blood urea nitrogen, creatinine, glucose, vitamin B12, and thyroid stimulating hormone); all results were within normal limits. All subjects fulfilled UK PD Society Brain Bank (UKPDSBB) clinical criteria for idiopathic PD as determined by a movement disorder specialist. [13]. A consensus panel determined the presence or absence of dementia, based on both neuropsychological testing and presence or absence of CI by informant history (Clinical Dementia Rating [14]). For this study, we focused our analysis on memory (Logical Memory II), Category Fluency (animal, vegetable), working memory/executive function (Trails B minus A), and processing speed (Digit Symbol) [15].

Research lumbar punctures (LPs) were performed as previously described [12]. Briefly, all CSF was obtained by lumbar puncture in the morning, was free of visual contamination by blood, had hemoglobin levels < 6.0 μ g/ml, and was flash frozen and then stored at -80° C in polypropylene cryovials until used. Coded samples were analyzed by individuals who did not know the corresponding clinical information. CSF samples were analyzed with a Luminex-based multianalyte profile (MAP) from Biosource (InVitrogen, CA) that included

total tau (t-tau), BDNF, interleukin 8, A β ₄₂, β ₂-microglobulin, vitamin D binding protein, apolipoprotein (apo) AII, and apoE as described previously [12].

Statistical Analysis

Associations between CSF biomarker and CI measurement and between these variables and age were determined using Spearman rank correlation coefficients (r). To determine if statistically significant associations were independent of age and gender, linear regressions of CI measurement on CSF biomarker were carried out with age and gender as covariates. Regression analyses were conducted on ranked CI measurements and CSF biomarkers to be consistent with the Spearman rank coefficients described above. Due to spurious findings that can arise when using ratios, statistical testing of the association between CI measurement and A β ₄₂/t-tau as a covariate were carried out using A β ₄₂ adjusted for t-tau (i.e. using both A β ₄₂ and t-tau as covariates in the linear regression models of CI measurements and reporting the significance of the coefficient for A β ₄₂). Significance was set at $p < 0.05$. Analyses were carried out using R 2.9.1 (www.R-project.org).

Results

Twenty-two subjects (17 male, 5 female) with PD and no dementia participated in this study. Mean Mini-Mental State Examination score (SD, range) was 28 (2, 25–30). The mean age at onset of motor symptoms was 59.2 years (11.6, 39–77). Mean Unified Parkinson's Disease Rating Scale (Part III) and Hoehn and Yahr scores at the time of neuropsychological testing were 21 (9, 7–42) and 2.5 (0.8, 1.5–4), respectively. The mean time between neuropsychological testing and LP was 0.6 years. The mean age at time of neuropsychological testing was 68.7 years (8.0, 56–81) and mean years of education was 16.5 (2.4, 12–20). Summary statistics for performance scores on the five neuropsychological tests are presented in the Table.

CSF samples were analyzed with a Luminex-based MAP as previously described [12]. Values were not elevated beyond age-matched controls (data not shown). Mean (range) levels for the markers of interest were 544.4 (222–1389) pg/ml for A β ₄₂, 284.6 (164– to 406) pg/ml for BDNF, and 136.6 (81–269) pg/ml for t-tau.

Neuropsychological test score correlations with A β ₄₂, t-tau, A β ₄₂/t-tau, and BDNF are presented in the Table and exemplary scatter plots of raw data are presented in the Figure. Results from all other members of our CSF MAP (not shown) did not show a significant correlation with any neuropsychological test outcome. A significant correlation was found between A β ₄₂ and performance on Digit Symbol ($r = 0.49$, $p = 0.02$), and between A β ₄₂/t-tau and performance on both Digit Symbol and Category Fluency (vegetable) ($r = 0.50$, $p = 0.02$ for both). Consistent with our hypothesis that AD biomarkers might be associated with AD-like cognitive impairment, we observed a trend for an association between lower A β ₄₂/t-tau and more impaired performance on delayed memory (Logical Memory II), a cognitive hallmark of AD, ($r = 0.34$), although this latter finding did not reach significance in this relatively small sample ($p = 0.12$). CSF BDNF concentration was significantly associated with Digit Symbol performance ($r = 0.54$, $p = 0.01$), but no other neuropsychological test result. Adjustment for age or gender attenuated several of the observed associations (Table). Associations remained between A β ₄₂/t-tau and Category Fluency (vegetable) after adjusting for age ($p = 0.04$) and between BDNF and Digit Symbol after adjusting for gender ($p = 0.04$); the association between BDNF and Digit Symbol was not quite significant after adjusting for age ($p = 0.06$). This was not unexpected, given that age was negatively correlated with Digit Symbol ($r = -0.46$, $p = 0.03$) and weakly negatively correlated with all other neuropsychological test results ($0.06 < p < 0.13$), except Trails B minus A where there was no correlation ($p = 0.4$).

Discussion

Cognitive impairment and dementia in patients with PD likely is a convergent phenotype that derives from multiple diseases that variably combine in a given individual [3]. Discrimination among these disease processes early in the course of illness will be very important to tailor treatments that suppress the processes associated with Lewy body disease, AD, or vascular disease. Furthermore, there is growing consensus that therapeutic interventions for illnesses that culminate in dementia will be most effective in pre-clinical and prodromal stages.

Here we tested the hypothesis that validated biomarkers linked to PD and AD would be associated with neuropsychological test performance in a group of non-demented PD patients. The strongest associations were observed between performance on Digit Symbol and CSF levels of $A\beta_{42}$, $A\beta_{42}/t\text{-tau}$, and BDNF, but not $t\text{-tau}$. We also observed a significant association between $A\beta_{42}/t\text{-tau}$ ratio and Category Fluency (vegetable), but no significant association between performance on Trails or Category Fluency (animal) with any of the CSF biomarkers. This pattern of results likely reflects, at least in part, the variance in difficulty in performing of these tasks. Performance on Digit Symbol is likely more sensitive to mild CI because it is supported by a number of component processes mediated by the frontal lobes. Notably, while motor-speed is also a determinant of Digit Symbol performance, other motor-dependent tasks (*i.e.*, Trails) and the motor UPDRS were not correlated with CSF biomarkers. Thus, it is likely the correlations observed with Digit Symbol were less dependent on motor speed and more dependent on cognitive performance. Other investigators have also observed that Digit Symbol and Category Fluency are sensitive to early cognitive change (*i.e.*, pre-dementia) in PD [16,17]. Examination of the co-variables of age and gender suggest that the association between $A\beta_{42}/t\text{-tau}$ and Digit Symbol or Category Fluency may not be independent. However, this statistical finding is difficult to interpret given the small sample size.

As expected, our results showed an association between neuropsychological test results and age. Studies in larger samples will be needed to assess further the potentially confounding influence of age and gender on the association between CSF biomarkers and cognitive performance in non-demented patients with PD, and to confirm the possible lack of association observed with tests other than Digit Symbol and Category Fluency.

Despite the small sample size, we were able to observe an association of CSF markers with cognitive test performance in non-demented PD patients. The directions of these associations were consistent with previous studies in neurodegenerative disease (*i.e.*, lower $A\beta_{42}$ and BDNF levels with poorer test performance). Also consistent with previous findings in PD-D [11], we did not find an association between CSF $t\text{-tau}$ levels and cognitive performance in our non-demented sample. While confirmation of these findings in a larger sample is necessary, they suggest it might be possible to use CSF biomarkers to characterize pathophysiologic processes underlying even mild CI in non-demented PD patients.

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Figure.

Scatter plots of data from the associations observed in non-demented patients with PD shown with loess curves. (A) Aβ₄₂ vs. Digit Symbol, (B) BDNF vs. Digit Symbol, (C) Aβ₄₂/t-tau vs. Category Fluency (vegetable), and (D) Aβ₄₂/t-tau vs. Digit Symbol.

Table

Correlations of Mini-Mental State Examination, Unified Parkinson's Disease Rating Scale (Part III), and neuropsychological test results with CSF biomarkers

		Spearman rank correlation coefficient			
	Median (range)	CSF A β ₄₂	CSF t-tau	CSF A β ₄₂ /t-tau**	CSF BDNF
MMSE	28 (25–30)	0.13	–0.30	0.32	0.13
UPDRS	17 (7–42)	–0.25	–0.12	–0.19	–0.06
Logical Memory II	15 (2–34)	0.12	–0.24	0.34	–0.07
Category Fluency (animal)	17 (7–24)	0.20	–0.24	0.29	0.34
Category Fluency (vegetable)	12 (5–20)	0.38	–0.36	0.50*†	0.38
Digit Symbol	39 (19–60)	0.49*	–0.10	0.50*	0.54*‡
Trails B minus A	52 (5–250)	–0.13	–0.01	–0.13	–0.23

* .01<p<.05, Spearman rank tests

† .01<p<.05 after adjusting for age in linear regression of log performance on log biomarker

‡ .01<p<.05 after adjusting for gender in linear regression of log performance on log biomarker

** Statistical inference carried out using A β ₄₂ and total tau as covariates in regression of test performance, and reporting significance for the A β ₄₂ coefficient