Published in final edited form as:

Mov Disord. 2010 November 15; 25(15): 2682–2685. doi:10.1002/mds.23287.

CSF A β_{42} and tau in Parkinson's disease with cognitive impairment

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Abstract

We tested the hypothesis that the CSF biomarker signature associated with Alzheimer's disease (AD) is present in a subset of individuals with Parkinson's disease and Dementia (PD-D) or with PD and Cognitive Impairment, Not Dementia (PD-CIND). We quantified CSF A β_{42} , total tau (T-tau), and phospho-tau (P181-Tau) using commercially available kits. Samples were from 345 individuals in seven groups (n): Controls $\leq$ 50 years (35), Controls $>$ 50 years (115), amnesic Mild Cognitive Impairment (aMCI) (24), AD (49), PD (49), PD-CIND (62), and PD-D (11). We observed expected changes in AD or aMCI compared with age-matched or younger controls. CSF A β_{42} was reduced in PD-CIND ($P < 0.05$) and PD-D ($P < 0.01$) while average CSF T-Tau and P181-Tau were unchanged or decreased. One-third of PD-CIND and one-half of PD-D patients had the biomarker signature of AD. Abnormal metabolism of A β_{42} may be a common feature of PD-CIND and PD-D.

Keywords

Parkinson's disease; cognitive impairment; CSF biomarkers; A β_{42} ; tau

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***Key:** 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Conflict of Interest: No author had a conflict of interest.

Introduction

Recent focus on biomarkers for Alzheimer's disease (AD) is fueled by now abundant data showing that processes of this disease start years prior to dementia or less severe forms of cognitive impairment (CI); the latter is commonly defined clinically as amnesic Mild CI (aMCI).¹ Currently, the most successful biomarker candidates for AD are PET imaging for fibrillar amyloid beta ($A\beta$), structural MRI, and quantification of cerebrospinal fluid (CSF) $A\beta_{42}$, total tau (T-tau), and tau phosphorylated at amino acid 181 (P181-tau; reviewed in ²). Indeed, increased CSF T-tau and P181-tau and decreased CSF $A\beta_{42}$ are characteristic of AD or aMCI in cross-sectional studies (reviewed in ² and ³), and similar changes are present in older individuals without CI who are at increased risk of conversion to MCI or AD.⁴⁻⁷ Emerging data suggest that neuroimaging and quantification of these CSF proteins are comparable in detecting processes of AD in preclinical settings.⁷⁻⁹

Parkinson's disease (PD) is now recognized commonly to include dementia (PD-D) and less severe forms of CI; in the PD research community the latter is commonly defined by a set of clinical criteria for "CI, Not Dementia" (CIND).¹⁰ Indeed, the point prevalence of dementia among patients with PD is approximately one-third, and approximately 75% of patients with PD develop dementia over 10 years.¹¹ Several hypotheses for CI in PD have been proposed, including subcortical processes, extension of Lewy body disease from brainstem to isocortical structures, and co-morbid AD; however, the extent to which each or a combination of these processes contributes CI in PD is unclear. The ability to identify patients with PD-CIND or PD-D deriving from AD versus other causes of dementia likely will be critical to organizing clinical trials and managing patients once disease-modifying therapies are developed. This issue has been addressed only in a few individuals by neuroimaging¹² and in CSF-based studies of limited number of relatively small disease groups that yielded conflicting conclusions.^{13, 14} Here we quantified CSF $A\beta_{42}$, T-tau, and P181-tau in 345 individuals to estimate the prevalence of co-morbid AD among patients with PD who did or did not have CI at the time of lumbar puncture.

Methods

The Human Subject Institutional Review Boards of Baylor College of Medicine, Oregon Health & Science University, the University of California at San Diego, 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. Exclusion criteria included moderate or heavy cigarette smoking (more than 10 packs/year), alcohol use other than social, and any psychotherapeutic drug use other than for treatment of AD or PD.

Controls were healthy volunteers who had normal cognitive performance on a battery of neuropsychological tests at the time of lumbar puncture as previously described.¹⁵ All controls had at least one year of follow-up (median of 3 years) without demonstrating any symptoms or signs of neurologic disease. AD¹⁶, PD¹⁷, and aMCI¹ were diagnosed by established criteria. The diagnosis of PD-D was determined by established criteria¹⁰ and included the "one-year rule" for differentiation from Dementia with Lewy Bodies, *viz.*, dementia must occur one year after onset of motor parkinsonism in PD-D. The diagnosis of PD-CIND was made in subjects with a diagnosis of PD and a clinical dementia rating of 0.5¹⁸ but without dementia as determined by PD-D criteria.

All CSF was obtained by lumbar puncture in the morning, was free of visual contamination by blood, had hemoglobin levels $< 6.0 \mu\text{g/ml}$, and was flash frozen and then stored at -80°C in polypropylene cryovials until used.¹⁹ All CSF samples from individuals in research cohorts at our institutions that met the above criteria were assayed for T-tau, P181-tau, and $\text{A}\beta_{42}$ concentrations using AlzBio3 Luminex kits from Innogenetics (Alpharetta, GA) by following exactly the manufacturer's instructions and were within the range of values reported by others.^{4, 7} Coded samples were analyzed by individuals who did not know any corresponding clinical information. Statistical analyses were performed with GraphPad Prism (San Diego, CA).

Results

In order to match age among disease groups and individuals with aMCI, we excluded 12 PD patients who were ≤ 50 years of age and divided Controls into $\leq$ or > 50 years old. There was no significant difference in concentrations (pg/ml) of any of the three CSF analytes between Controls > 50 yr and Controls ≤ 50 yr. Table 1 summarizes data from the remaining 333 CSF samples used in primary analyses. As expected, the AD group had significantly decreased CSF $\text{A}\beta_{42}$ ($P < 0.001$) and significantly increased CSF T-tau ($P < 0.001$) and P181-tau ($P < 0.001$) concentrations compared to Controls > 50 yr. Similar to others, we observed increased CSF T-tau ($P < 0.05$) and P181-tau ($P < 0.001$) concentrations in individuals with aMCI.^{4, 7} Figure 1A plots individuals' CSF $\text{A}\beta_{42}$ vs. P181-tau levels for both Control groups, aMCI, and AD.

CSF P181-tau/ $\text{A}\beta_{42}$ is a convenient means to summarize the coincidental increase in CSF P181-tau and decrease in CSF $\text{A}\beta_{42}$ that is characteristic of AD. Assuming that clinically silent AD is uncommon in Controls ≤ 50 years, we and others have previously used this ratio in Controls ≤ 50 years to define an upper cutoff value for normal CSF P181-tau/ $\text{A}\beta_{42}$.^{5, 6} Using this approach, 3% of Controls ≤ 50 years, 25% of Controls > 50 years, 92% of individuals with aMCI, and 96% of patients with AD had abnormally increased CSF P181-tau/ $\text{A}\beta_{42}$. Similar results were obtained using CSF T-tau/ $\text{A}\beta_{42}$ (not shown). These results validated this method for detecting pre-clinical and clinical AD.

Among the groups of patients with PD, CSF $\text{A}\beta_{42}$ levels ranged from normal in those without CI, to progressively lower values in patients with PD-CIND ($P < 0.05$) or PD-D ($P < 0.01$). In contrast to patients with aMCI or AD, CSF T-tau levels were unchanged in the three PD groups and CSF P181-tau levels were significantly *decreased* in patients with PD ($P < 0.05$) or PD-CIND ($P < 0.01$). Figure 1B plots individuals' CSF $\text{A}\beta_{42}$ vs. P181-tau to display the strikingly different biomarker signature among patients with PD, PD-CIND, or PD-D compared to patients with aMCI or AD. Using the same approach as above, we estimated that 15% of patients with PD, 29% of patients with PD-CIND, and 45% of patients with PD-D had abnormally elevated CSF P181-tau/ $\text{A}\beta_{42}$.

Unlike MCI and both groups with dementia, there were eight patients (age range) with PD (35 to 50 years) and four patients with PD-CIND (40 to 50 years) who were ≤ 50 years old. None of the CSF concentrations for any of the three analytes was out of the range reported for the corresponding group of older patients.

Discussion

Quantification of CSF $\text{A}\beta_{42}$, T-tau, and P181-tau provides a validated means to assess processes of AD in patients with dementia or CI, and even in older individuals who are cognitively normal.²⁻⁹ Applying this tool to 119 patients with PD and a spectrum of CI, we observed progressively lower CSF $\text{A}\beta_{42}$ concentrations in patients with PD, PD-CIND, or

PD-D. In combination with exquisite studies of others,⁸ these data suggest that progressive CI in patients with PD may be associated with increased deposition of fibrillar A β in cerebrum, and that this process might be demonstrable with PET imaging.⁹

T-tau increases in CSF in AD and other degenerative and destructive diseases of brain and is widely thought to signify damage to neurons. Although CSF T-tau levels trended to lower values in the PD-D group, these were not significant and thereby concordant with the results of some¹⁴ but not others who observed an increase in average CSF T-tau in patients with PD-D.¹³ In contrast, we observed that average P181-tau concentrations in PD and PD-CIND groups were significantly 20% lower than age-matched controls and this result differs from others who have reported no difference or increased average CSF P181-tau in these groups.^{13, 14} CSF P181-tau is more difficult to interpret than T-tau since its levels presumably reflect at least two potentially related mechanisms, cellular processes that lead to phosphorylation and release from damaged neurons. The reasons for these discrepant results among studies are not clear. However, one interpretation of our results is that patients with PD, PD-CIND, and PD-D may have less neuron damage than patients with aMCI or AD and may have suppression of those biochemical processes that lead to threonine-181 phosphorylation on tau.

We estimated that approximately one-third of patients with PD-CIND and slightly less than one-half of patients with PD-D had abnormally increased CSF P181-tau/A β ₄₂, although there was no distinct pattern of sub-populations (see Figure 1B). This stands in sharp contrast to the > 90% of patients with aMCI or AD who had abnormally increased CSF P181-tau/A β ₄₂. One possible explanation for these results is that the majority of patients with PD and CI do not have co-morbid AD.

Our results suggest that validated CSF biomarkers for processes of AD may be helpful in identifying those patients with PD and co-morbid AD. Further investigation of the neuropsychological profile and possible risk from inheritance of the ϵ 4 allele of *APOE* is needed for this group of patients with PD and CI. However, our results also indicate that this is a minority of patients with PD-CIND or PD-D, and underscore the need for further research into other more common causes of CI and dementia in patients with PD.

Acknowledgments

This work was supported by grants from the NIH (ES004696, NS057567, AG025327, AG033398, NS060252, NS062684, AG05136, AG08017 and AG08671), the Michael J. Fox Foundation, and the Nancy and Buster Alvord Endowment. This support had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. We thank Dr. Kathleen Montine for editorial assistance.

Financial Disclosure: This work was supported by grants from the NIH (ES004696, NS057567, AG025327, AG033398, NS060252, NS062684, AG05136, AG08017 and AG08671), the Michael J. Fox Foundation, and the Nancy and Buster Alvord Endowment. This support had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Full Financial Disclosure of all Authors for the Past Year. Financial support was received from the NIH, the VA, and the Michael J. Fox Foundation.

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Figure 1. Scatter plots of CSF Aβ₄₂ and P181-tau concentrations

Individuals' CSF Aβ₄₂ and P181-tau concentrations for (A) both Control groups, subjects with amnesic Mild Cognitive Impairment (MCI), and patients with Alzheimer's Disease (AD), and for (B) patients with Parkinson's disease (PD) without cognitive impairment (CI), with CI but Not Dementia (PD-CIND), or dementia (PD-D).

Table 1
Age and Biomarker Results for Each Group

Group (n)	Age (yr) Mean±SD	Disease Duration (yr) Mean±SD	CDR Global Median	Hoehn- Yahr Score Median	Concentration in CSF (pg/ml) Median (25 th to 75 th Interquartile Range)		
					Aβ ₄₂	T-Tau	P181-Tau
Control ≤ 50 yr (35)	32 ± 8	---	0	---	420 (359 – 492)	58 (47 – 69)	21 (17 – 25)
Control > 50 yr (115)	68 ± 10	---	0	---	378 (284 – 505)	60 (50 – 73)	25 (19 – 39)
MCI (24)	68 ± 7	---	0.5	---	386 (284 – 514)	82* (54 – 123)	66*** (46 – 112)
AD (49)	68 ± 10	10 ± 5	2	---	216*** (158 – 247)	88*** (67 – 126)	51*** (39 – 72)
PD (41)	64 ± 10	8 ± 6	0	2	322 (282 – 401)	54 (44 – 67)	20* (17 – 25)
PD-CIND (58)	66 ± 8	8 ± 7	0.5	2.5	313* (225 – 389)	53 (44 – 66)	20** (17 – 22)
PD-D (11)	71 ± 8	16 ± 6	2	3.5	220** (187 – 275)	33 (30 – 72)	17 (12 – 30)

Kruskal-Wallis test comparing six groups (Controls > 50 yr and five disease groups) for Aβ₄₂, T-tau, or P181-tau concentrations (pg/ml) had P < 0.0001 for all three comparisons Dunn's corrected repeat paired comparisons with Controls > 50 yr had

Abbreviations: CDR (Clinical Dementia Rating), MCI (Mild Cognitive Impairment), AD (Alzheimer's disease), PD (Parkinson's disease), CIND (Cognitive Impairment Not Dementia), and (D) Dementia

*** P < 0.001
** P < 0.01
* P < 0.05.