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DJ-1 and αSYN in LRRK2 CSF do not correlate with striatal dopaminergic function

Min Shi[a,*], **Amy Furay**[a,*], **Vesna Sossi**[b], **Jan O. Aasly**[c], **Jeff Armaly**[a], **Yu Wang**[a,d], **Zbigniew K. Wszolek**[e], **Ryan J. Uitti**[e], **Kazuko Hasegawa**[f], **Teruo Yokoyama**[f], **Cyrus P. Zabetian**[g,h,i], **James B. Leverenz**[h,i,j,k], **A. Jon Stoessl**[l], and **Jing Zhang**[a,†]

[a]Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA

[b]Department of Physics & Astronomy, University of British Columbia, Vancouver Hospital and Health Sciences Centre, Purdy Pavilion, Vancouver, BC V6T2B5 Canada

[c]Department of Neurology, St. Olavs Hospital, Trondheim, Norway

[d]Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[e]Department of Neurology, Mayo Clinic Florida, Jacksonville, FL, USA

[f]Department of Neurology, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

[g]Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

[h]Parkinson's Disease Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

[i]Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

[j]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA

[k]Mental Illness Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

[l]Pacific Parkinson's Research Centre, University of British Columbia & Vancouver Coastal Health, Vancouver, BC V6T2B5 Canada

Abstract

Previous studies demonstrated decreased levels of DJ-1 and α-synuclein (αSYN) in human cerebrospinal fluid (CSF) in patients with Parkinson's disease (PD), but neither marker correlated with PD severity, raising the possibility that they may be excellent progression markers during early or preclinical phases of PD. Individuals carrying the leucine-rich repeat kinase 2 (LRRK2)

†Address correspondence to: Jing Zhang, Department of Pathology, University of Washington School of Medicine, HMC Box 359635, 325 9th Ave, Seattle, WA 98104, USA. Phone: 1-206-897-5245, Fax: 1-206-897-5452, zhangj@uw.edu.
*The authors have contributed equally.

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gene mutation are at increased risk for PD, and the phenotype of LRRK2 patients is almost identical to sporadic PD. To determine whether dopaminergic dysfunction in the basal ganglia, as determined by positron emission tomography (PET) scans, correlates with CSF levels of DJ-1 and αSYN during preclinical stages, Luminex assays were used to analyze CSF samples from asymptomatic LRRK2 mutation carriers, along with carriers who presented with a clinical diagnosis of PD. The data revealed no statistically significant relationship between PET scan evidence of loss of striatal dopaminergic function and the CSF biomarkers DJ-1 and αSYN, except for a weak correlation between DJ-1 and MP binding, suggesting that the use of these potential biomarkers on their own to screen LRRK2 gene mutation carriers for PD is not appropriate.

Keywords

Parkinson's Disease; LRRK2; gene mutation; biomarker; DJ-1; α-synuclein

1. Introduction

A majority of dopaminergic cell bodies in the substantia nigra are lost before clinical symptoms of PD are evident, so there is an urgent need for preclinical biomarkers that correlate with dopaminergic cell loss and other PD pathology. Previously, we and others reported decreased levels of DJ-1 and α-synuclein (αSYN) in human cerebrospinal fluid (CSF) in several large cohorts of PD patients. However, there was no statistically significant relationship between biomarker levels and PD severity in sporadic PD patients (Hong et al., 2010), suggesting that there might be a "floor" effect and these biomarkers may alter more significantly during early stages of the disease, i.e. correlate with early PD progression. Developing biomarkers that predict early phase disease onset and progression may help in the development of treatments designed to slow disease progression and enable treatment when the disease is most responsive to therapy. Since carriers of a mutated gene encoding leucine-rich repeat kinase 2 (LRRK2) are at increased risk for PD (Adams et al., 2005; Cookson, 2010), they are an ideal population for studying disease onset and progression.

2. Methods

Symptomatic (n=8) or asymptomatic (n=18) individuals from Japan, the United States, and Norway carrying the LRRK2 mutated gene were included in this study; all had standard informed consent, clinical examination, and tests. Subjects were PET scanned with three different radiolabeled tracers (^{18}F-6-fluoro-L-dopa, ^{11}C-(±)-α-dihydrotetrabenazine, and ^{11}C –d-*threo*-methylphenidate) to determine the uptake and decarboxylation of levodopa in the striatum, as well as vesicular monoamine and plasmalemmal dopamine transporter binding. CSF samples were collected via lumbar puncture; Luminex assays measuring αSYN and DJ-1 were used to analyze biomarkers. Statistical analysis was performed using PASW Statistics software (SPSS Inc, Chicago, IL, USA). Correlation between CSF αSYN and DJ-1 levels and PET measurements was evaluated using Kendall's rank correlation coefficient; overall group differences in CSF biomarkers were analyzed using Mann-Whitney Wilcoxon rank sum tests. For more detail, see the Supplemental Methods section.

3. Core data/results

Consistent with previous studies, abnormal (decreased) PET changes were observed in asymptomatic and symptomatic subjects (Adams et al., 2005). Since previous reports suggest that blood contamination of CSF (indexed by CSF hemoglobin levels) affects αSYN and DJ-1 levels (Hong et al., 2010), three subjects (2 w/PD, 1 asymptomatic) with hemoglobin levels >250 ng/mL were eliminated from further analysis. As graphically

represented in Supplemental Figure 1 (DJ-1 only) and summarized in Supplemental Tables 1 and 2 (DJ-1 and αSYN), there was a slight trend toward a positive correlation between CSF DJ-1 and PET measurements, particularly DTBZ and MP. Next, to determine if such a relationship existed in carriers of the G2019S mutation, the most common form of LRRK2 genetic mutation, we analyzed only G2019S mutation carriers (3 w/PD, 8 asymptomatic) but found no relationship between PET scan results and CSF biomarkers, except for a weak correlation between DJ-1 and MP. Consistent with our previous study in sporadic PD patients (Hong et al., 2010), there was no significant correlation between DJ-1 or αSYN levels in CSF and PD severity (UPDRS motor scores and H&Y stage); there were also no differences between groups in either potential biomarker, probably due to limited case numbers (see Supplemental Data section).

4. Discussion

The purpose of this study was to determine if CSF levels of αSYN and DJ-1 are suitable preclinical biomarkers for detecting early phase PD by correlating them with PET scan data measuring progressive loss of striatal dopaminergic function in primarily asymptomatic LRRK2 mutation carriers. These data indicate that CSF αSYN and DJ-1 are not significantly correlated with dopamine dysfunction/cell loss in all LRRK2 gene mutation carriers combined and only a weak correlation was found in the G2019S subset of carriers alone. Although previous studies have suggested that the total levels of αSYN and DJ-1 in CSF are potential diagnostic biomarkers for sporadic PD, with relatively high sensitivity and specificity (Hong et al., 2010), the results of the present study suggest that on their own, they may not be appropriate biomarkers for preclinical or early phase PD diagnosis and/or disease progression, at least in the population of LRRK2 gene mutation carriers, **which might be different from typical sporadic PD patients**. Although the sample size is small, the present data set strongly suggest that efforts should be directed toward identifying other potential biomarkers, including specific αSYN and DJ-1 species/isoforms, with more robust predicative validity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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