Parkinsonism and Related Disorders xxx (2017) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Homocysteine and cognitive function in Parkinson's disease

Nicole Licking [a, b], Charles Murchison [a], Brenna Cholerton [c], Cyrus P. Zabetian [d, e], Shu-Ching Hu [d, e], Thomas J. Montine [f], Amie L. Peterson-Hiller [a, b], Kathryn A. Chung [a, b], Karen Edwards [g], James B. Leverenz [h], Joseph F. Quinn [a, b, *]

[a] Department of Neurology, Oregon Health and Science University, Portland, OR, United States
[b] Parkinson's Disease Research, Education, and Clinical Center, Portland Veterans Affairs Medical Center, Portland, OR, United States
[c] Department of Psychiatry & Behavioral Sciences, University of Washington, Seattle, WA, United States
[d] Parkinson's Disease Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, United States
[e] Department of Neurology, University of Washington, Seattle, WA, United States
[f] Department of Pathology, Stanford University, Palo Alto, CA, United States
[g] Department of Epidemiology, University of California at Irvine, United States
[h] Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, OH, United States

ARTICLE INFO

Article history:
Received 10 February 2017
Received in revised form
31 July 2017
Accepted 7 August 2017

Keywords:
Cognition
Parkinson's disease
Movement disorders
Dementia

ABSTRACT

Introduction: Increased plasma homocysteine (HC) is a risk factor for dementia in the general population. Levodopa therapy causes increased plasma HC, but it remains unclear whether elevated plasma HC is associated with cognitive impairment in Parkinson's disease (PD).

Methods: The study population includes all participants in the Pacific Northwest Udall Center (PANUC) Clinical cohort at the time of the study, consisting of 294 individuals with PD who had a standardized neuropsychological assessment and plasma collection for HC measurement. We tested the hypothesis that elevated plasma HC is inversely related to cognitive function in patients with PD.

Results: As expected, plasma HC was positively associated with age, disease duration, disease severity, and levodopa usage, while cognitive function was associated with age, education, gender, and *APOE* genotype, so subsequent analyses controlled for these covariates. When plasma HC was dichotomized as normal (<14 μmol/L) or elevated (≥14 μmol/L), subjects with hyper-homocysteinemia had lower scores on Digit Symbol ($p = 0.031$), Hopkins Verbal Learning Task (HVLT) Delayed Recall ($p = 0.004$), and semantic verbal fluency ($p = 0.049$). When examined as a continuous variable, plasma HC was inversely associated with HVLT Delayed Recall ($p = 0.009$)) and semantic verbal fluency ($p = 0.004$), but was not significantly related to Digit symbol, Trail-making test, Judgment of Line Orientation, phonemic verbal fluency, MMSE, or MOCA. When analysis was restricted to non-demented subjects ($n = 231$), the findings were unchanged.

Conclusions: We conclude that plasma HC is significantly associated with some aspects of cognitive function in PD, and may represent a treatable risk factor for cognitive decline in PD.

1. Introduction

Dementia is a common and disabling outcome in Parkinson's disease (PD) [1], so identification of treatable risk factors for this complication is urgently needed. Elevated plasma homocysteine (HC) may be such a risk factor, as hyperhomocysteinemia is associated with dementia in the general population [2] and HC-lowering strategies may have beneficial effects on cognition if initiated early, before dementia is established [3,4]. This may be particularly relevant to dementia risk in PD, as levodopa usage promotes hyperhomocysteinemia [5]. However, the literature on plasma HC and cognitive impairment in PD is mixed, with some reports finding impaired cognition in PD patients with hyperhomocysteinemia [6–10], while others find no relationship between HC and dementia in PD [11–13]. The discrepancies in the literature may be attributed to sample size or to the comprehensiveness of cognitive testing. We consequently re-visited this relationship in a large ($n = 294$) cohort of PD patients who underwent

* Corresponding author. 3181 SW Sam Jackson Park Rd, Portland, OR 97239, United States.
E-mail address: quinnj@ohsu.edu (J.F. Quinn).

http://dx.doi.org/10.1016/j.parkreldis.2017.08.005
1353-8020/

comprehensive neuropsychological testing in a study of cognitive outcomes in PD. This allowed us to not only test the hypotheses that elevated plasma HC is associated with cognitive dysfunction in patients with PD (as other studies have done), but to test whether elevated plasma HC is associated with impairments in specific cognitive domains. We also examined whether HC effects on cognitive function are related primarily to plasma HC levels or to levodopa dosage.

2. Methods

2.1. Participants

Participants from the Pacific Northwest Udall Center (PANUC) were enrolled using methods previously described [14]. Briefly, the PANUC Clinical Consortium comprises prevalent cohorts of participants with idiopathic PD assembled at the University of Washington/VA Puget Sound and Oregon Health Sciences University/VA Portland. All participants met the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) clinical diagnostic criteria for idiopathic PD [15]. Exclusion criteria included failure to meet UKBB criteria for PD or history of other neurologic disorders that would significantly impact cognition, such as large-vessel stroke or severe traumatic brain injury. All participants volunteer to undergo detailed clinical and neuropsychological evaluation, including recording of age, gender, education, medications, date of diagnosis. This study included the first 294 eligible individuals with PD enrolled in PANUC. The neuropsychological battery includes tests of memory, executive function, visuospatial function, and language function, as well as other tests selected for their sensitivity in PD [14]. A cognitive diagnosis (not impaired, mild cognitive impairment [MCI], or dementia) was assigned to each subject at a consensus conference [14] held shortly after the clinical and neuropsychological assessment, based on the full battery of neuropsychological tests, in accordance with Movement Disorder Society (MDS) recommendations [16,17]. Consensus diagnosis is reached by a team of neuropsychologist and neurologists after review of neuropsychological testing and collateral history including Clinical Dementia Rating, as previously described [14]. In order to minimize the statistical effects of multiple comparisons, the analysis of relationships between cognitive function and plasma HC was confined to a subset of neuropsychological tests that we have found to be informative in other studies [18–22].

Participants also have plasma collected and frozen at each research visit, on the day of neuropsychological assessment. For this study, HC was measured by gas chromatography in banked plasma samples collected on the day of neuropsychological testing and frozen until testing.

2.2. Standard protocol approvals, registrations, and patient consents

The institutional review boards at all institutions approved the study, and all subjects (or their legal surrogates) provided written informed consent.

2.3. Statistical analysis

To fully evaluate the effects of hyperhomocysteinemia, the biomarker levels were considered both as a continuous variable and as a discrete factor contrasting subjects with normal plasma HC to those with elevated levels greater than 14 μmol/L.

Primary analysis used ordinary least squares to assess the relationships between plasma HC levels and the cognitive function outcomes. Reported models were corrected for covariates known or expected to be associated with cognition and HC levels including: age, gender, length of PD duration, MDS-UPDRS-III score, Hoehn & Yahr stage, years of education, being a carrier of the *APOE* ε4 allele (*APOE4*), and cognitive status (cognitively intact, MCI, dementia). Entacapone use was not included in the model because a regression analysis showed no evidence of an effect of entacapone use upon homocysteine levels in this cohort. Due to the well-established relationship between levodopa use and elevated homocysteine, causal mediation analysis was performed to identify the proportion of cognitive dysfunction directly attributable to levodopa use and the proportion of decline due to mediation through hyperhomocysteinemia. This enabled testing of the hypothesis that while levodopa use causes hyperhomocysteinemia, it is the mediating effects of hyperhomocysteinemia which in fact promote cognitive decline.

Model integrity was evaluated using standard diagnostics to identify overly influential outliers and leverage points and confirm linear regression assumptions. A multiple comparison adjustment was done to account for the large number of modeled outcomes of interest. Specifically, a Holm-Sidak stepwise correction was applied to the set of 11 p-values taken from the final covariate-corrected multiple regression models to more confidently assert the significance of the relationships between HC levels and cognitive outcomes.

3. Results

Plasma HC did not significantly differ among the three groups (cognitively intact, MCI, and PD dementia). Subsequent analyses compared groups defined by normal vs. elevated plasma HC.

Table 1 presents the characteristics of all 294 study participants, as well as a comparison of clinical characteristics in those with normal HC levels (HC $\leq$ 14) and those with elevated HC (HC > 14). Average age of all participants was 68.0 ± 9.1 years and 68% were male. The average duration of PD was 9.95 ± 6.8 years with a median Hoehn and Yahr score of 2.5 (IQR = 2–3), with 184 subjects (63%) receiving L-DOPA treatment. Fifty-six had a consensus diagnosis of “cognitively intact”, 175 had PD-MCI, and 63 had PD dementia (The relatively high prevalence of MCI and dementia are consistent with the long median duration of disease in this population).

The participants with elevated HC levels were older (72 ± 8 vs 66 ± 9 years, $p < 0.001$), had a longer duration of disease (11 ± 8 vs 9 ± 7 years, $p = 0.026$), higher Hoehn and Yahr (2.72 ± 0.8 vs 2.49 ± 0.7, $p = 0.017$), and higher MDS-UPDRS part III score (32.8 ± 13 vs 26.9 ± 13, $p < 0.001$) (Table 1). Subjects with elevated HC were also more likely to be receiving L-DOPA treatment ($RR = 1.89$, $p = 0.001$). This effect of treatment on elevated HC was specifically associated with L-DOPA dose ($z = 2.15$, $p = 0.03$) and not Entacapone ($z = 0.55$, $p = 0.59$). Analyses of relationships between HC and cognitive function consequently included each of these factors as covariates, as well as other factors known to influence cognitive status, such as years of education and *APOE* ε4carrier status. (There was no relationship between *APOE* ε4 carrier status and plasma HC.)

Individuals with elevated plasma HC had significantly lower cognitive scores in multiple domains in the absence of correction for confounding factors (Table 2). However, in fully corrected models (i.e., both controlled for covariates and corrected for multiple comparisons, indicated by p_{adj}), significant differences were seen only on WAIS digit symbol, ($p_{adj} = 0.031$), semantic verbal fluency ($p_{adj} = 0.049$), and HVLT delayed recall ($p_{adj} = 0.004$) (Table 2). Analysis of continuous relationships between HC level

Please cite this article in press as: N. Licking, et al., Homocysteine and cognitive function in Parkinson's disease, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.08.005