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Publication Date

2017-11-01

DOI

10.1016/j.parkreldis.2017.08.005

Peer reviewed

HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Parkinsonism Relat Disord. 2017 November ; 44: 1–5. doi:10.1016/j.parkreldis.2017.08.005.

Homocysteine and Cognitive function in Parkinson's

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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

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Relevant conflicts of interest/financial disclosures: nothing to report.

(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.

Keywords

cognition; Parkinson's disease; movement disorders; dementia

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] [7] [8] [9] [10], while others find no relationship between HC and dementia in PD [11] [12] [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 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.

METHODS

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] [19] [20-22].

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.

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.

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.

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≤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 and cognitive function also found a significant inverse correlation between HC and semantic verbal fluency ($p_{adj}=0.004$), HVLT immediate recall ($p_{adj}=0.012$) and HVLT delayed recall ($p_{adj}=0.009$). No other cognitive tests were related to HC in either analysis (i.e., HC as a dichotomous or continuous variable).

Additional analyses were undertaken in order to control for the possibility that demented patients may have higher plasma HC levels as a complication of dementia (e.g., due to dietary changes in demented patients). All of the findings reported for the entire group were significant even when adjusting for clinical diagnoses of cognitive impairment, or when limiting the analysis to the non-demented subjects (n=231).

Mediation analysis furthered implicated the specific effects of hyperhomocysteinemia on the reduced performance on the cognitive outcomes. Using the same fully corrected models

described above, it was observed in the elevated homocysteine group that only the mediating effects of hyperhomocysteinemia, but not direct effects of levodopa dosage, were significantly related to impaired performance in semantic verbal fluency (direct: p=0.29; mediated: p=0.04) and HVLT delayed recall (direct: p=0.17; mediated: p<0.01). Similarly, when assessing the continuous relationships between HC and cognitive function, the direct effects of levodopa dosage were not significant while mediation due to hyperhomocysteinemia was significant for semantic verbal fluency (direct: p=0.41; mediated: p=0.01), HVLT immediate recall (direct: p=0.58; mediated: p=0.01), and HVLT delayed recall (direct: p=0.14, mediated: p<0.01). These results suggest that while levodopa usage may indeed be related to elevated HC, it is the specific influence of hyperhomocysteinemia that is related to a decline of cognitive ability.

DISCUSSION

We found that plasma HC is associated with selected aspects of cognitive function in PD even after correcting for multiple confounding factors. Specifically, semantic verbal fluency and verbal memory function were inversely related to plasma HC, considered as either a dichotomous (high vs normal) or continuous variable, while other aspects of language and visuospatial function were not related to plasma HC. The relationship between executive function and plasma HC was less clear, as one measure (Digit Symbol) was lower in patients with hyper-homocysteinemia, while another (Trail-making) was not, and neither of these scores was associated with HC as a continuous variable. We hypothesize that the association of plasma HC with specific cognitive tests is due to the relative sensitivity of those tests as markers of cognitive decline in PD, rather than reflecting a causal relationship between plasma HC and specific neural systems.

These findings are consistent with some published reports confirming a relationship between HC and cognitive function in PD [6] [7] [8] [9] [10], but in contrast to other published reports refuting any association [11] [12] [13]. Notably, the relatively few studies failing to find a relationship between HC and cognition in PD involved relatively small sample sizes (N=51 and 89 PD patients [11] [12]) in comparison to the study reported here, which represents the largest sample of PD patients ever reported with both plasma HC and cognitive status. This study is also unique in examining associations between plasma HC and specific cognitive domains, which may also contribute to the fact that a relationship between HC and cognitive function was detectable in this study but not in others that relied on cognitive diagnoses or more general measures like MMSE or MOCA[11] [13].

The determinants of plasma HC include B vitamin levels and levodopa dosage. The lack of plasma B vitamin data is a relative weakness of this study. However, the effect of levodopa dosage was investigated in a mediation analysis which supports the hypothesis that elevated HC itself promotes cognitive decline in PD. This hypothesis is plausible in light of basic science evidence that elevated levels of HC are toxic to both neurons [23] and endothelial cells[24], and by clinical studies showing that elevated plasma HC predicts both neurofibrillary tangles and vascular pathology at brain autopsy [25], and that HC-lowering interventions slow cognitive decline in non-PD MCI patients[3] [4]. The hypothesis that HC

is potentially harmful to PD patients is further supported by clinical studies showing that elevated HC predicts rate of brain atrophy in PD [26].

However, the correlations demonstrated in this cross-sectional analysis fall short of demonstrating a causal relationship between elevated HC and cognitive decline in PD. Although the study cited above found accelerated brain atrophy in PD patients with elevated plasma HC, a second study found no evidence that plasma HC predicted the cognitive outcome over 2 years [27]. A larger, long-term, prospective study may help to establish whether plasma HC predicts outcomes, and one such study, COPPADIS-2015 (COhort of Patients with PArkinson's DIsease in Spain, 2015) is reportedly under way [28]. However, the ultimate test of whether plasma HC is a treatable risk factor for cognitive decline in PD will require a randomized trial of a homocysteine-lowering intervention in PD subjects at risk of cognitive decline.

Acknowledgments

This research was supported by the Pacific Northwest Udall Center (NINDS P50 NS062684) and the Department of Veterans Affairs Northwest Parkinson's Disease Research, Education, and Clinical Care Center (PADRECC). Funding for homocysteine measurements was provided by the Paul and Elizabeth Duffy Family Trust. The funding sources did not provide scientific input for the study.

Funding sources: NINDS NS062684 (Pacific Northwest Udall Center), Department of Veterans Affairs Northwest Parkinson's Disease Research, Education, and Clinical Care Center (PADRECC), Paul and Elizabeth Duffy Family Trust.

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Highlights

- Elevated plasma homocysteine was associated with poor cognitive performance in PD.
- Homocysteine is inversely correlated with tests of memory and verbal fluency in PD.

Table 1

Study Population Characteristics

	All Subjects (N=294)	Normal Homocysteine (N=207)	Elevated Homocysteine (N=87)	Arm Comparison
Age (years)	68.0 (9.1)	66.4 (8.9)	72.0 (8.4)	t=19.9 (p<0.001)
Gender - male (%)	200 (68.0%)	134 (64.7%)	66 (75.9%)	RR=1.46 (p=0.075)
Parkinson's duration (years)	9.95 (6.893)	9.34 (6.54)	11.42 (7.51)	t=2.25 (p=0.026)
UPDRS-3 score	28.6 (13.1)	26.9 (12.9)	32.8 (12.6)	t=3.54 (p<0.001)
Hoehn & Yahr score	2.555 (0.7478)	2.485 (0.7224)	2.724 (0.7849)	t=2.41 (p=0.017)
Education (years)	16.05 (2.745)	16.09 (2.776)	15.94 (2.679)	t=−0.43 (p=0.67)
Current L-dopa use (%)	184 (62.6%)	117 (56.5%)	67 (77%)	RR=1.89 (p=0.001)
Dopamine agonist use (%)	93 (31.6)	72 (34.8%)	21 (29.2%)	RR=1.09 (p=0.66)
ApoE4 carriers (%)	65 (23.0%)	47 (23.7%)	18 (21.2%)	RR=0.97 (p=0.76)
Mild Cognitive Impairment	175 (59.5%)	126 (60.9%)	49 (56.3%)	RR=0.90 (p=0.52)
Dementia	63 (21.4%)	39 (18.9%)	24 (27.6%)	RR=1.12 (p=0.12)

Table 2

Cognitive outcomes in normal vs. elevated homocysteine

	All Subjects (N=294)	Normal Homocysteine (N=207)	Elevated Homocysteine (N=87)	Naive Comparison (Uncorrected)	Covariate Corrected Comparison*
Digit Symbol Test	38.4 (12.02)	39.9 (12)	34.6 (11.28)	t=3.53 (p=0.001)	p=0.031
Semantic verbal fluency (animals)	18.1 (6.34)	18.9 (6.36)	16.2 (5.89)	t=3.51 (p=0.001)	p=0.067
Semantic verbal fluency (vegetables)	12.4 (4.58)	13 (4.51)	10.9 (4.4)	t=3.67 (p=<0.001)	p=0.049
Phonemic verbal fluency (FAS)	38.2 (12.63)	39.2 (12.89)	35.9 (11.74)	t=2.06 (p=0.041)	NS
Hopkins Verbal Learning - Immediate	21.1 (6.36)	22 (6.1)	18.6 (6.4)	t=3.81 (p=<0.001)	NS
Hopkins Verbal Learning - Delayed	6.8 (3.77)	7.4 (3.43)	5 (4.08)	t=4.33 (p=<0.001)	p=0.004
Judgment of Line Orientation	11.8 (2.42)	11.9 (2.42)	11.6 (2.42)	t=1.01 (p=0.313)	NS
Letter-Number Sequence Test	9.8 (3.1)	9.9 (3.07)	9.4 (3.18)	t=1.08 (p=0.283)	NS
MMSE	27.6 (2.17)	27.7 (2.17)	27.4 (2.16)	t=1.11 (p=0.27)	NS
MOCA	24.3 (3.52)	24.3 (3.42)	24.2 (3.76)	t=0.09 (p=0.929)	NS
Trails B (sec)	142 (87.17)	136.1 (88.73)	156.4 (81.98)	t=−1.87 (p=0.064)	NS

Values are mean (SD)

*Corrected p-values taken from covariate corrected models with Holm-Sidak correction for multiple comparisons