Volume 29, Number 6
November - December 2006

Plasma Homocysteine Levels and Parkinson Disease: Disease Progression, Carotid Intima-media Thickness and Neuropsychiatric Complications

Sharon Hassin-Baer, MD,† Oren Cohen, MD,*† Eli Vakil, PhD,‖ Ben-Ami Sela, PhD,‡ Zeev Nitsan, MD,* Roseline Schwartz, MSc,* Joab Chapman, MD, PhD,* and David Tanne, MD,*§*

Abstract

Objective:
To determine whether plasma homocysteine (Hcy) levels are associated with clinical characteristics, neuropsychological and psychiatric manifestations and cardiovascular comorbidity in patients with Parkinson disease (PD).

Background:
Elevated Hcy levels are linked to atherosclerosis, vascular disease, depression, and dementia. Patients with PD treated with L-dopa have been shown to have elevated Hcy levels.

Design/Methods:
Idiopathic PD patients were evaluated using the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, Parkinson Psychosis Rating Scale, Beck Depression Inventory, Frontal Assessment Battery, Mini-Mental Status Examination, and several tests for frontal type cognitive functions. Fasting blood samples were collected for the measurement of Hcy, and carotid B-mode ultrasound was performed to measure intima-media thickness of the common carotid arteries.

Results:
Seventy-two consecutive PD patients (46 men; average age, 68.7 ± 11.6 years; average disease duration, 7.0 ± 4.7 years) were recruited. All but 10 patients were treated with L-dopa. The average level of Hcy was 16.4 ± 7.8 μmol/L, and 38.9% of the patients had Hcy level above the reference range (>15.0 μmol/L). The Hcy levels were associated with PD duration as they were with L-dopa treatment duration but were not associated with the parameters of disease severity or with L-dopa dose. The Hcy levels were associated neither with the common carotid intima-media thickness nor with cardiovascular morbidity. No association was found between Hcy and the neuropsychiatric features of PD such as depression, cognitive performance, or psychosis.

Conclusions:
Hyperhomocystinemia is common in L-dopa–treated PD patients but was not associated with neuropsychological complications (depression, dementia, and cognitive decline associated with frontal lobe functioning or psychosis), enhanced disease severity, or vascular comorbidity.

Key Words: Parkinson disease, neuropsychiatric complications, homocysteine

(*Clin Neuropharmacol* 2006;29:305–311)

Nonmotor complications in Parkinson disease (PD) become increasingly important as disease progresses. Among them are cognitive decline, dementia, depression, and psychosis.[1,2] Their pathogenesis in PD is multifactorial. Elevated levels of homocysteine (Hcy), a sulfur-containing amino acid that occupies a central location in the metabolic pathways of thiol compounds, were shown in epidemiological and experimental studies to be linked with several conditions associated with vascular pathology including coronary artery disease, vascular dementia, and ischemic stroke.[3–5] Neurodegenerative processes have also been linked to elevated Hcy, including cognitive decline and Alzheimer disease.[6–9] Moreover, genetic and clinical data suggest roles for folate deficiency and Hcy in the pathogenesis of some psychiatric disorders such as depression and schizophrenia.[10,11]

Plasma Hcy levels are elevated in patients with PD treated with L-dopa,[12–16]

*Department of Neurology and †Parkinson's Disease and Movement Disorders Clinic, Sagol Neuroscience Center, ‡Department of Chemical Pathology and §Stroke Center, Chaim Sheba Medical Center, Tel Hashomer, Affiliated to Sackler School of Medicine, Tel Aviv University, Israel and ‖Department of Psychology, Bar Ilan University, Ramat-Gan, Israel.

Address correspondence and reprint requests to Sharon Hassin-Baer, MD, Department of Neurology and Parkinson's Disease and Movement Disorders Clinic, Chaim Sheba Medical Center, Tel Hashomer, 52621, Israel; E-mail: shassin@post.tau.ac.il

DOI: 10.1097/01.WNF.0000236763.16032.60

resulting from the increased production of *S*-adenosylhomocysteine during the metabolism of L-dopa by catechol-*O*-methyltransferase. The clinical significance of L-dopa–induced elevation of Hcy in PD on vascular disease, the disease course, or the development of the cognitive and psychiatric complications is not known. The aim of the current study was to examine the hypothesis that elevated plasma Hcy in PD is associated with measures of progression of PD, cognitive and neuropsychiatric complications, increased carotid intima-media thickness, and cardiovascular comorbidity.

PATIENTS AND METHODS

Consecutive patients with PD were prospectively recruited between September 2003 and January 2004 from the Movement Disorders Clinic and the Neurology Service at Sheba Medical Center. All the patients were diagnosed with idiopathic PD according to the UK bank criteria. The local ethics committee approved the study protocol, and all the patients had to give their informed consent before their inclusion in the study. Exclusion criteria included patients that are not fluent Hebrew speakers or having other central nervous system disorders (eg, normotensive hydrocephalus and brain tumor), psychiatric disorders (eg, major depression and schizophrenia), and prominent cerebrovascular disease and patients that had functional neurosurgical procedures for PD.

All the patients underwent systematic assessments of demographics, vascular risk factors, atherothrombotic manifestations (stroke, transient ischemic attack, ischemic heart disease, and peripheral vascular disease). Parkinson disease duration, predominant manifestations, presence of motor complications, types of medications, and drug regimen including dose and duration of L-dopa treatment were recorded. The physical status was measured using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (the motor scale), in the "on" condition in patients experiencing motor fluctuations, and the Hoehn and Yahr scale, both "on" and "off" in patients experiencing motor fluctuations.

Neuropsychiatric disturbances were evaluated using the Beck Depression Inventory,[17] an Apathy Scale for PD, and the Parkinson Psychosis Rating Scale.[18] Patients were asked about having had hallucinations or delusions and presence of visual impairment. Sleep disturbances and daily somnolence were also documented.

The global cognitive functioning was assessed using the Mini-Mental Status Examination.[19] Attention was assessed using the digit span forward and backward tests,[20] the Trail-making test (parts A and B), and the number-cancellation test.[21] Verbal memory was examined using the Hebrew version of Rey–auditory verbal learning test (the immediate recall, leaning, and delayed parts).[22] Visual memory was assessed using the Rey-Osterrieth complex figure test, including copy, immediate, and delayed parts.[21] The frontal lobe functioning was examined using the Frontal Assessment Battery[23] and tests for phonemic and semantic word fluency.[21]

In the morning, after 12 hours of fasting, blood samples were drawn from a peripheral vein in plastic vacuum tubes containing EDTA. Within 10 minutes, the samples were centrifuged for 15 minutes, 300*g* at 10°C, and plasma was stored at −20°C. The Hcy levels were measured within 3 months using an automated high-performance liquid chromatography method with reverse phase separation and fluorescent detection, using NaBH4/monobromobimane reduction followed by monobromobimane derivation. A laboratory technician, who was blinded to any clinical data, performed all the tests.

For carotid ultrasound examination, common carotid artery intima-media thickness (IMT), a measure of atherosclerosis, was measured at the far wall of both common carotid arteries using an ATL ultrasound and dedicated software for image acquisition, semiautomatic measurements, and storage (M'Ath-Std, Metris, France).

Statistical Method

Patients were stratified into 3 groups by tertiles of Hcy level (first tertile, <12.5 μmol/L; second tertile, 12.5–16.7 μmol/L; and third tertile, >16.7 μmol/L). Mean values of the quantitative variables were compared among the groups using 1-way analysis of variance or Kruskal-Wallis test according to their distribution. With regard to the analyses of cognitive function, a general linear model of analysis of variance was used to obtain multivariable-adjusted mean differences in scores among those with different levels of Hcy. To control for confounding in the model, we included, in addition to the Hcy level, the following variables: age and time duration of PD as continuous covariates and sex as a categorical covariate. Significant levels were set at $P < 0.05$. All statistical analyses were performed with statistical software (SPSS, version 12.0).

RESULTS

Seventy-two patients with PD (46 men and 26 women) were included. Their mean age was 68.7 ± 11.6 years (range, 42–96 years), and the mean PD duration was 7.0 ± 4.7 years (range, 0.5–18 years). Their characteristics are shown in Table 1. The average plasma Hcy concentration was 16.4 ± 7.8 μmol/L (range, 6.9–45.1 μmol/L).

TABLE 1. Characteristics of the Patients in Total and According to Hcy Tertiles

	All Patients	First Tertile (<12.5 μmol/L)	Second Tertile (12.5–16.7 μmol/L)	Third Tertile (<16.7 μmol/L)	*P*
No. patients	72	23	24	25	
Hcy level (mean [SD]), μmol/L	16.4 (7.8)	10.2 (1.8)	14.0 (1.0)	24.2 (8.2)	
Age, (mean [SD], y	68.7 (11.6) (range, 42–96)	69.9 (12.3)	67.0 (11.4)	69.3 (11.4)	0.66
No. male subjects, %	46 (63)	10 (44)	18 (75)	18 (72)	0.05
Education (mean [SD]), y	12.0 (3.7)	10.9 (4.5)	13.2 (3.4)	11.8 (2.8)	0.09
No. patients treated with L-dopa (n [%])	62 (86)	18 (78)	20 (83)	24 (96)	0.18
Disease duration (mean [SD]); tertiles: median, (interquartile range), y	6.7 (4.7) (0.5–27)	5 (3–7)	6 (4–10.8)	8 (6–11)	0.003
L-dopa treatment duration (mean [SD]); tertiles: median, (interquartile range), y	5.1 (4.1) (0.5–18)	4 (3–7)	6.5 (4.3–10.8)	7.5 (5.0–10)	0.01
Motor UPDRS (mean [SD])	24.9 (12.4) (range, 5–56)	22.4 (10.4)	21.7 (12.0)	27.3 (13.2)	0.22
Hallucinations (n [%])	14 (19.4)	2 (8.7)	4 (16.7)	8 (32)	0.11
Delusions (n [%])	13 (18.1)	1 (4.3)	4 (16.7)	8 (32)	0.44

Continuous variables are presented as mean (SD) and range, and categorical variables are presented as number (%).

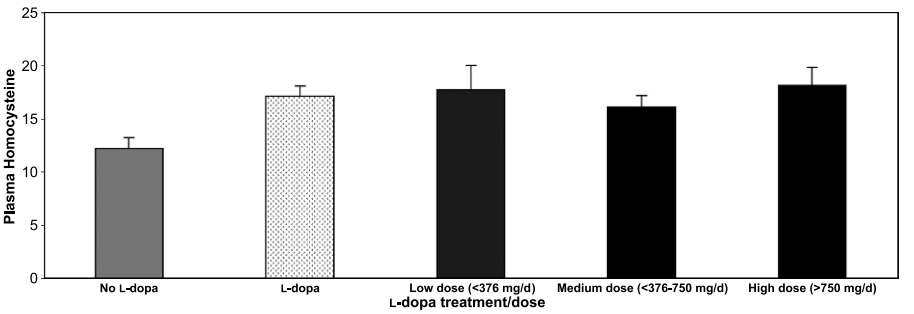

FIGURE 1. Plasma Hcy levels and L-dopa dose.

Twenty-eight patients (38.9%) had elevated Hcy (Hcy levels, >15.0 μmol/L); all except for one were among the patients treated with L-dopa. The average Hcy level tended to be higher among patients treated with L-dopa (n = 62) than among untreated patients (n = 10) (17.0 ± 8.1 μmol/L vs. 12.3 ± 3.4 μmol/L; $P = 0.068$). Comparisons of the Hcy level according to L-dopa dose (Fig. 1) did not demonstrate a dose effect of L-dopa on Hcy level. An association was found between L-dopa treatment duration and the level of Hcy ($P = 0.036$).

Hcy levels did not correlate with the age of the patients. We could not demonstrate significant associations between Hcy levels and disease severity according to motor section of the UPDRS. We did find a positive association with disease duration ($P = 0.003$; also seen when analysis was performed for only the 62 patients treated with L-dopa) (Table 2). This could account for the association of Hcy level with L-dopa treatment duration. The Hcy levels were not associated with vascular comorbidity such as coronary heart disease or with history of cerebrovascular disease, such as stroke or transient ischemic attack (data not shown in tables). No significant associations were identified between Hcy levels and the presence or history of depression, use of antidepressants, hallucinations, or use of antipsychotics or the presence of intellectual decline according to the part 1 of UPDRS ($P > 0.05$ for all). Using the Kruskal-Wallis test for comparison of 3 or more unmatched groups, we found no association between the Hcy level and Hohen and Yahr stages in the off and in the on states. No significant correlations were found between Hcy levels and any of the neuropsychological or psychiatric tests, including psychiatric and behavioral features, attention, verbal memory, frontal lobe function, or global cognitive function (Table 2).

Among the patients undergoing assessment of the carotid IMT (n = 45), the average IMT of both common carotid arteries was 0.80 ± 0.17 mm. Carotid IMT did not differ between patients with normal Hcy (n = 24; average, 0.79 ± 0.17 mm) and those with elevated Hcy (n = 19; average, 0.81 ± 0.17 mm). Carotid IMT correlated with the age of the patients ($r = 0.55$, $P < 0.001$) but did not correlate with any PD-related factors such as disease duration or severity or with measures of neuropsychiatric complications. Comparing the average IMT of the patients in the 3 Hcy tertiles, correcting for age, sex, and disease duration, yielded similar results.

DISCUSSION

Our main findings are that elevated concentrations of plasma Hcy were common (39%) among PD patients and were associated with the use of L-dopa, but plasma Hcy was not associated with neuropsychological complications (depression, dementia, frontal-type cognitive decline, or psychosis), enhanced disease severity, carotid IMT, or vascular comorbidity in our cohort of PD patients.

It has been previously established that L-dopa treatment, rather than the disease

CLINICAL NEUROPHARMACOLOGY 309
Volume 29, Number 6
November - December 2006

TABLE 2. Behavioral Features and Results of Neuropsychological Testing According to Hcy Tertiles

	First Tertile	Second Tertile	Third Tertile	*P* (corrected)
No. patients, (maximum)	23	24	25	
Psychiatric and behavioral features				
Parkinson's psychosis rating scale (mean [SD])	7.1 (1.7)	7.6 (1.7)	8.2 (2.1)	0.62
Apathy scale (mean [SD])	15.5 (5.2)	17.6 (4.3)	17.8 (3.8)	0.04
Beck Depression Inventory score (mean [SD])	14.9 (13.4)	15.6 (11.2)	13.7 (9.5)	0.99
Global cognitive function				
Mini-Mental Status Examination (mean [SD])	26.2 (3.2)	26.3 (3.0)	26.1 (3.8)	0.71
Attention				
Trail-making (part A) (mean [SD]), s	158.6 (194.2)	112.3 (74.2)	114.4 (88.1)	0.48
Trail-making (part B) (mean [SD]), s	223.4 (152.8)	254.9 (163.1)	246.3 (163.3)	0.96
Digit forward (mean [SD])	7.9 (2.1)	7.9 (2.4)	7.5 (2.7)	0.59
Digit backward (mean [SD])	5.3 (2.4)	5.6 (2.8)	5.3 (2.3)	0.96
Verbal memory				
Rey-AVLT (trial 1) (mean [SD])	3.8 (2.7)	4.8 (2.4)	4.6 (2.0)	0.20
Rey-AVLT (trial 5) (mean [SD])	8.8 ± 3.9	9.5 ± 3.2	8.8 ± 2.6	0.40
Rey-AVLT (trial 8) (mean [SD])	8.3 (4.7)	7.7 (3.6)	6.7 (2.7)	0.55
Frontal lobe function				
Frontal Assessment Battery	14.4 (2.8)	14.8 (2.7)	13.2 (3.7)	0.14
Phonemic word fluency (average no. words)	6.9 (3.3)	7.8 (3.3)	7.7 (3.2)	0.51
Semantic word fluency (average no. words)	13.8 (7.5)	15.3 (5.2)	13.5 (5.4)	0.37

Adjustments were made for age and time duration of PD as continuous covariates and for sex as a categorical covariate.

AVLT indicates auditory verbal learning test.

itself, is associated with elevated Hcy, and the metabolic pathways underlying this phenomenon are well documented. The MTHFR genotype and vitamin status have minor contributory effects to Hcy levels as well.[12,24,25]

To date, there is limited evidence that L-dopa–induced hyperhomocystinemia has any detrimental effects on PD patients. Elevated plasma Hcy is, however, well known to serve as a marker for vascular diseases[3,4] and is associated with carotid IMT.[6,24,26] One cross-sectional study[27] found that L-dopa–associated Hcy elevations were associated with a 1.7-fold increased prevalence of coronary artery disease, and another[28] reported its association with hypertrophy of the carotid intima-media complex. Plasma Hcy levels among our PD cohort were not associated with carotid IMT nor with prevalent vascular comorbidity. If L-dopa–induced hyperhomocystinemia is a causal risk factor for vascular complications in PD, then one would expect epidemiological evidence of greater Hcy-associated diseases in PD patients. There is, however, no convincing data showing that cardiovascular disease or stroke is more prevalent in PD than in controls.[29,30]

Elevated Hcy levels have been identified as risk factors for cognitive decline and Alzheimer disease[6–9] and may be linked to the pathogenesis of some psychiatric disorders

such as depression and schizophrenia.[10,11] The relative risk of developing dementia in PD is 4 to 6 times that of an age-matched population, but not all the mechanisms underlying it are elucidated.[5] In a recent study, mood and cognition outcomes were worse in PD patients with elevated Hcy levels, although the physical status was not significantly worse.[14] In our study, we did not find an effect of elevated Hcy on any of the neuropsychological complications of PD (depression, dementia, frontal-type cognitive decline, or psychosis). Also, we could not demonstrate any association between Hcy levels and measures of disease severity.

The lack of any significant associations in our PD cohort between elevated Hcy levels and neuropsychological complications, enhanced disease severity, carotid IMT, or vascular comorbidity may potentially be caused by limited statistical power and type II error. The absence of any apparent effect, however, argues against any major detrimental effect. Because of the high public health implications of potentially preventing a reversible cause for PD-related complications, but potential hazards of unproven interventions, this hypothesis should be further explored in large prospective cohort studies and randomized clinical trials.

REFERENCES

1. Aarsland D, Andersen K, Larsen JP, et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 2003;60:387–392.
2. Poewe W, Luginger E. Depression in Parkinson's disease: impediments to recognition and treatment options. *Neurology* 1999;52(Suppl 3):S2–S6.
3. Sasaki T, Watanabe M, Nagai Y, et al. Association of plasma homocysteine concentration with atherosclerotic carotid plaques and lacunar infarction. *Stroke* 2002;33:1493–1496.
4. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 1969;56:111–128.
5. Eikelboom JW, Lonn E, Genest J, et al. Homocysteine and cardiovascular disease: a critical review of the epidemiologic evidence. *Ann Intern Med* 1999;131: 363–375.
6. Dufouil C, Alperovitch A, Ducros V, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. *Ann Neurol* 2003;53:214–221.
7. Prins ND, Den Heijer T, Hofman A, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. *Neurology* 2002;59: 1375–1380.
8. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002; 346:476–483.
9. McIlroy SP, Dynan KB, Lawson JT, et al. Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. *Stroke* 2002;33: 2351–2356.
10. Levine J, Stahl Z, Sela BA, et al. Elevated homocysteine levels in young male patients with schizophrenia. *Am J Psychiatry* 2002;159: 1790–1792.
11. Bottiglieri T, Laundy M, Crellin R, et al. Homocysteine, folate, methylation, and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatry* 2000;69:228–232.
12. Miller JW, Selhub J, Nadeau MR, et al. Effect of L-dopa on plasma homocysteine in PD patients: relationship to B-vitamin status. *Neurology* 2003;60: 1125–1129.
13. O'Suilleabhain PE, Bottiglieri T, Dewey RB, et al. Modest increase in plasma homocysteine follows levodopa initiation in Parkinson's disease. *Mov Disord* 2004;19:1403–1408.
14. O'Suilleabhain PE, Sung V, Hernandez C, et al. Elevated plasma homocysteine level in patients with Parkinson disease: motor, affective, and cognitive associations. *Arch Neurol* 2004;61:865–868.
15. Rogers JD, Sanchez-Saffon A, Frol AB, et al. Elevated plasma homocysteine levels in patients treated with levodopa: association with vascular disease. *Arch Neurol* 2003;60:59–64.
16. Kuhn W, Roebroek R, Blom H, et al. Elevated plasma levels of homocysteine in Parkinson's disease. *Eur Neurol* 1998;40:225–227.
17. Leentjens AF, Verhey FR, Luijckx GJ, et al. The validity of the Beck Depression Inventory as a screening and diagnostic instrument for depression in patients with Parkinson's disease. *Mov Disord* 2000;15:1221–1224.
18. Friedberg G, Zoldan J, Weizman A, et al. Parkinson Psychosis Rating Scale: a practical instrument for grading psychosis in Parkinson's disease. *Clin Neuropharmacol* 1998;21:280–284.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
20. Wechsler D. *Wechsler Memory Scale*, 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
21. Lezak M. *Neuropsychological Assessment*, 3rd ed. New York, NY: Oxford University Press; 1995.
22. Vakil E, Blachstein H. Rey AVLT: developmental norms for adults and the sensitivity of different memory measures to age. *Clin Neuropsychol* 1997; 11:345–355.
23. Dubois F, Slachevsky A, Litvan A, et al. The FAB: a frontal assessment battery at bedside. *Neurology* 2000;55:1621–1626.

CLINICAL NEUROPHARMACOLOGY 311

Volume 29, Number 6
November - December 2006

24. Seshadri S, Wolf PA. Homocysteine and the brain: vascular risk factor or neurotoxin? *Lancet Neurol* 2003;2:11.
25. Blandini F, Fancellu R, Martignoni E, et al. Plasma homocysteine and l-dopa metabolism in patients with Parkinson disease. *Clin Chem* 2001;47: 1102–1104.
26. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 1993;87(Suppl 3):II56–II65.
27. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? *J Neurol Neurosurg Psychiatry* 1995;58:293–299.
28. Nakaso K, Yasui K, Kowa H, et al. Hypertrophy of IMC of carotid artery in Parkinson's disease is associated with L-DOPA, homocysteine, and MTHFR genotype. *J Neurol Sci* 2003;207:19–23.
29. Jellinger K. Prevalence of stroke in Parkinson's disease. *Mov Disord* 2003;18:723–724.
30. Korten A. Stroke and idiopathic Parkinson's disease: does a shortage of dopamine offer protection against stroke? *Mov Disord* 2001;16: 119–123.