Elevated Plasma Homocysteine Level in Patients With Parkinson Disease

Motor, Affective, and Cognitive Associations

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Background: An elevated plasma homocysteine (Hcy) level has been prospectively associated with an increased risk of vascular and degenerative dementias. An Hcy elevation is prevalent in patients with Parkinson disease (PD) in part because levodopa metabolism produces Hcy. The clinical relevance of an elevated Hcy level in patients with PD is unknown.

Objective: To determine if hyperhomocysteinemia in patients with PD is associated with depression or with cognitive or physical impairments.

Design: Ninety-seven people with a mean (SD) PD duration of 3.6 (1.6) years completed the Beck Depression Inventory, a battery of 11 cognitive tests, and the motor and function components of the Unified Parkinson's Disease Rating Scale. Normalized scores for the affective, cognitive, and physical measures were compared between those with a normal Hcy level (n=66) and those with hyperhomocysteinemia (n=31) (Hcy level, >1.89 mg/L [>14 µmol/L]), controlling for age, sex, disease duration, and treatment.

Results: Subjects with an elevated Hcy level were slightly older (68 vs 62 years), but had similar plasma concentrations of vitamin B12 and folate. Hyperhomocysteinemic patients were more depressed (P=.02) and had worse cognition (P<.01), but the physical measure did not differ.

Conclusions: Patients with PD and hyperhomocysteinemia are more likely to be depressed and to perform worse on neuropsychometric tasks compared with normohomocysteinemic patients. Further research is warranted to see if hyperhomocysteinemia is a reversible risk factor for neuropsychiatric burden in patients with PD.

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The rate of progression of Parkinson disease (PD) varies widely. The change in the motor score of the Unified Parkinson's Disease Rating Scale during the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) trial is an example: for subjects randomized to placebo, the 9-point standard deviation was the same as the mean change. One fifth of PD patients develop dementia in the first 5 years of the disease, while many patients observed for more than a decade remain free of dementia. Approximately one third of patients become disabled within 5 years, another third within 10 years, and many of the others go more than 15 years without becoming disabled. Most of the variance in rate and extent of neurodegeneration in patients with PD is unexplained.

An elevated circulating concentration of homocysteine (Hcy) is a risk factor for vascular disease, Alzheimer disease and dementia, and cortical and hippocampal atrophy. Homocysteine concentrations above 1.89 mg/L (>14 µmol/L) are associated with a 25% decrease in cognitive performance, even among elderly people without dementia.

We hypothesize that an elevated Hcy level, which is common in patients with PD who are taking levodopa, is a risk factor for more rapid progression of motor and mental impairment in PD. Because an elevated Hcy level can usually be lowered by vitamin supplementation, such findings have potential therapeutic implications for ameliorating rates of clinical deterioration.

METHODS

SUBJECTS

Subjects were recruited from the database of patients seen during the past 4 years in the...
The study was approved by the institutional review board. All except 3 subjects with levels of up to 1.5 mg/dL (133 µmol/L) was taken, and the DNA was purified. Genotyping for the 5,10-

methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism was performed using restriction endonucleases. Subjects were considered to have a C/C genotype if the Hcy concentration was greater than 1.89 mg/L. This cutoff was used as the influential prior study. Analysis of covariance was used (GLM procedure; SAS Institute Inc, Cary, NC), controlling for daily levodopa dose, age, sex, and duration of PD.

Blood (10 mL) was drawn in an EDTA tube on the morning following a 12-hour fast and 12 hours off of PD drugs (if any). The blood was immediately centrifuged at 5000 rpm for 5 minutes, and the supernatant was frozen at −20°C. The buffy coat was removed, 24 were taking levodopa, 31 were receiving dopamine agonist monotherapy, and 30 were taking a combination of levodopa and dopamine agonists. Renal impairment, which can result in an elevated Hcy level, was not prevalent: the creatinine level was 1.2 mg/dL or less (≤106 µmol/L) in all except 3 subjects with levels of up to 1.5 mg/dL (133 µmol/L). The study was approved by the institutional review board.

**RESULTS**

The Hcy concentration ranged from 0.74 to 4.03 mg/L (5.5–29.8 µmol/L), with an outlier at 17.13 mg/L (126.7 µmol/L). The outlier was a 73-year-old man with untreated PD who was taking B vitamins and had a C/C MTHFR genotype; he was excluded from the ensuing analyses of Hcy level predictors. The mean (SD) Hcy level for the remainder of subjects was 1.73 (0.74) mg/L (12.8 [5.5] µmol/L). The mean plasma vitamin B12 concentration was 473 (range, 102-1700) pg/mL (349 [range, 75-1254] pmol/L), while the mean plasma folate concentration was 11.4 (range, 0.97-19.86) ng/mL (25.9 [range, 2.20-45.00] nmol/L).

The Hcy level was correlated with age (r = 0.28, P = .006) and creatinine concentration (r = 0.32, P = .001), but not with disease duration (r = 0.03, P = .70). The Hcy level correlated inversely with plasma vitamin B12 concentration in patients not using levodopa (r = −0.34, P = .04), but the association was absent among subjects treated with levodopa (r = −0.04, P = .80). The Hcy level did not correlate with plasma folate level in the whole cohort (r = −0.06, P = .60), nor in the group not treated with levodopa.

Fifty-two subjects were using daily B vitamin supplements. These subjects had higher plasma concentrations of vitamin B12 and folate (P < .001 for both) compared with subjects not taking vitamin supplements, but their Hcy concentrations were not different than nonusers (P = .40). The Hcy level was lower in women than in men (1.50 vs 1.83 mg/L [11.1 vs 13.5 µmol/L]; P < .01), and this was not explained by differences in age. When the model included plasma creatinine level, which was lower in women, the sex difference disappeared. The MTHFR genotype was C/C in 59 persons, C/T in 31, and T/T

**PREDICTORS OF HCY LEVEL**

Three clinical domains (affect, cognition, and physical status) were evaluated using 14 clinical tests. Mood was assessed with the modified Beck Depression Inventory. The cognitive evaluation consisted of the Mini-Mental State Examination, the phonemic and animal fluency portions of the Controlled Oral Word Association Test, the Stroop color-word task, block design and digit span subtests from the Wechsler Adult Intelligence Scale–Third Edition, the sum of trials 1 through 3 (immediate recall) and trial 4 (delayed recall) of the Hopkins Verbal Learning Test–Revised, the copy portion of the Rey-Osterrieth Complex Figure, and immediate and delayed recall of the Rey-Osterrieth Complex Figure. Scoring for the digit span and block design subtests and for the phonemic and animal fluency portions of the Controlled Oral Word Association Test used age and education correction tables. Stroop color-word task, Hopkins Verbal Learning Test–Revised, and Rey-Osterrieth Complex Figure scoring used age correction tables.

Physical status was measured using the Unified Parkinson’s Disease Rating Scale, parts 2 (activities of daily living scale) and 3 (motor scale).

**STATISTICAL ANALYSIS**

z Scores for each of the 14 clinical tests were calculated so that the mean for each was 0, and scores 1 SD worse and better than average were −1 and 1, respectively. For analysis, the 14 z scores were reduced to 3: physical function (averaged z scores of the Unified Parkinson’s Disease Rating Scale, parts 2 and 3), mood (Beck Depression Inventory score), and cognition (averaged z scores of the 11 psychometric tests). The group whose Hcy level was normal was compared with the group whose Hcy concentration was greater than 1.89 mg/L. This cutoff was used as the longstanding standard in our laboratory, and this is the cutoff used in an influential prior study.

Analysis of covariance was used (GLM procedure; SAS Institute Inc, Cary, NC), controlling for daily levodopa dose, age, sex, and duration of PD.

**CLINICAL EVALUATION**

Three clinical domains (affect, cognition, and physical status) were evaluated using 14 clinical tests. Mood was assessed with the modified Beck Depression Inventory. The cognitive evaluation consisted of the Mini-Mental State Examination, the phonemic and animal fluency portions of the Controlled Oral Word Association Test, the Stroop color-word task, block design and digit span subtests from the Wechsler Adult Intelligence Scale–Third Edition, the sum of trials 1 through 3 (immediate recall) and trial 4 (delayed recall) of the Hopkins Verbal Learning Test–Revised, the copy portion of the Rey-Osterrieth Complex Figure, and immediate and delayed recall of the Rey-Osterrieth Complex Figure. Scoring for the digit span and block design subtests and for the phonemic and animal fluency portions of the Controlled Oral Word Association Test used age and education correction tables. Stroop color-word task, Hopkins Verbal Learning Test–Revised, and Rey-Osterrieth Complex Figure scoring used age correction tables.
in 5, and unavailable in 2. The Hcy level was not different among those with and without T alleles.

Fifty-four subjects were using levodopa, with a mean (SD) dosage of 532 (279) mg/d based on a 0.8 multiplier for the controlled-release formulation. Subjects using levodopa were older than those not taking levodopa (68 vs 62 years, \( P = 0.04 \)), and the duration of PD was longer by 0.8 years \( (P = 0.02) \). The plasma Hcy level was higher among levodopa users vs nonusers (1.84 vs 1.58 mg/L \([13.6 \text{ vs } 11.7 \mu mol/L] \); \( P = 0.01 \)). Among the subjects using levodopa, higher Hcy concentrations were associated with higher levodopa doses \((r = 0.35, P < 0.01)\) and with higher plasma levodopa concentrations \((r = 0.42, P < 0.002)\). Thirty-one subjects had Hcy concentrations above 1.89 mg/L.

**CLINICAL OUTCOMES**

Mood \((P = 0.02)\) and cognition \((P < 0.01)\) outcomes were worse in subjects with an elevated Hcy level, while the physical status was not significantly worse \((P = 0.20)\). The magnitude of the estimated difference in z scores was 0.5 for mood (ie, 0.5 of a standard deviation) and 0.4 for cognition. Subsequent analyses showed that for every one of the 14 component tests, the hyperhomocysteinemic cohort had a negative z score, although \( P = 0.05 \) for only 4: the block design subtest, the animal fluency portion of the Controlled Oral Word Association Test, the copy portion of the Rey-Osterrieth Complex Figure, and the Unified Parkinson’s Disease Rating Scale, part 3.

**SHORT-TERM EFFECTS OF FOOD AND DRUGS ON PLASMA HCY LEVEL**

A difficult phlebotomy prevented postprandial samples for 2 subjects. In the others, the plasma Hcy level was slightly lower in the second sample, but this did not reach significance by the paired \( t \) test \((0.12 \text{ mg/L} \ [0.9 \mu mol/L]; \ SD \ 0.57 \text{ mg/L} \ [4.2 \mu mol/L]; \ P = 0.05)\). The difference between the first and second samples was not affected by treatment with levodopa \((P = 0.50)\). The difference between samples was not a function of sex, age, disease duration, or MTHFR genotype. There was a trend toward a greater postprandial decrease in Hcy level among subjects taking vitamin supplements \((P = 0.10)\), and subjects with a higher plasma folate concentration also had a greater postprandial Hcy decrease \((r = -0.22, P = 0.04)\).

**COMMENT**

An elevated plasma Hcy concentration \((>1.89 \text{ mg/L})\) was present in 31 (32%) of our 97 patients with fairly recent onset PD. This is consistent with previous reports.

An elevated Hcy level is most likely due to the prevalent use of levodopa: as in previous studies, \(9,11,12\) the patients taking levodopa had higher Hcy levels than those not taking levodopa. In animal models, levodopa increases the plasma Hcy level, \(10,12\) and we and others \(26,27\) have found that starting levodopa therapy in patients with PD results in substantial Hcy elevations within 3 months. This may reflect levodopa’s drain on methylation reserves: methyl donor depletion, and an elevated concentration is a risk factor for stroke, cardiac disease, and dementia. \(3,6\) Clinical associations of elevated Hcy level in PD patients have not, to our knowledge, previously been described. We report worse mood and cognitive function in PD patients whose Hcy level is elevated. We found, in addition, trends toward worse motor and cognitive status on all of the clinical measures. While subjects with an elevated Hcy level were older by approximately 4 years, their worse clinical outcomes do not seem to be due to factors such as age or disease duration because these factors were controlled for in the study.

Our findings, if confirmed, indicate that disease burden in PD patients, such as poor motor performance, depression, and cognitive deterioration, is associated with a high Hcy level. A causal link in either direction is feasible: a systemic Hcy elevation, or the genetic-environmental factors underlying such an elevation, may predispose to cerebrovascular disease or otherwise impair neuronal function. Alternatively, worse parkinsonism or depression may predispose to an Hcy elevation as an epiphenomenon, due to dietary, activity, or medication factors such as high doses of levodopa. The nonavailability of historical data about Hcy level in these patients limits interpretation of the association reported herein. A causal link could be supported by a prospective study showing the rate of disease progression as a function of Hcy concentration early in the disease. We are observing this cohort to see if the rate of future deterioration is a function of baseline Hcy level. The main impetus for pursuing this hypothesis is the possibility of identifying a reversible cause for PD-related complications. The Hcy levels can be lowered and methyl donor deficiencies can be improved using B vitamin supplementation. Such an intervention was not effective for secondary prophylaxis of stroke. \(30\) In principle, this should not preclude a trial of vitamins in PD patients early in the course of levodopa-induced hyperhomocysteinemia: adverse effects in this setting may be more preventable than symptomatic vasculopathy is reversible.

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