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Is There the Preventive Effect of COMT-inhibitor on Parkinson's Disease Associated with Dementia?

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Background: Elevated homocysteine (hcy) levels are associated with dementia, which is a frequent non-motor symptom of Parkinson's disease (PD). High levels of hcy in PD patients treated with levodopa are thought to result from increased synthesis during the metabolism of levodopa by COMT, and that use of a COMT-inhibitor may reduce hcy levels. In this study, we sought to clarify the effects of COMT-inhibitors on dementia in PD patients.
Methods: Thirty-eight PD patients without dementia (PDwoD), 35 PD patients with dementia (PDD), and 48 controls were enrolled in this study. All subjects underwent neuropsychological testing and a neurological examination. The hcy levels were measured in all subjects, and the relationship between hcy levels and dementia was evaluated in two PD groups (those that underwent treatment with levodopa-alone versus treatment with levodopa plus a COMT-inhibitor).
Results: Patients in the PDD group showed higher hcy levels than patients in the PDwoD group, though there was no significant difference in the hcy level between PDwoD patients and healthy controls. Regarding the effects of a COMT-inhibitor, there was no correlation between hcy levels in the 2 PD subgroups, indicating that there were no significant effects of the COMT-inhibitor on PDD. In addition, the odds ratio for PDD with the use of a COMT-inhibitor was 0.864 (95% CI = 0.342-2.180).
Conclusions: These results are in agreement with previous studies in that levodopa treatment in PD patients leads to elevated hcy concentrations. COMT-inhibitors, on the other hand, had no preventive effect on cognitive impairment in PD patients.

Key Words: *Parkinson's disease, Dementia, COMT-inhibitor, Homocysteine*

INTRODUCTION

Dementia is a frequent manifestation of advanced Parkinson's disease (PD) [1]. The incidence of dementia in patients with PD is 2-6 times higher than in the general population, and increases with disease duration [2]. The exact cause and underlying neurological mechanism behind the development of dementia in PD are still unknown. Serum hcy has various neuronal and endothelial cellular toxicities, and hyperhomocysteinemia is associated with cardiovascular, ocular, cerebrovascular, and neurodegenerative disease [1, 3]. Elevated hcy levels have also been reported to correlate with depression, mild cognitive impairment, and dementia in the elderly population, and hcy levels have been found to predict rates of cognitive decline in healthy elderly individuals [4, 5]. Therefore, elevated serum hcy levels have been implicated in the pathogenesis of cognitive impairment such as vascular dementia and Alzheimer's disease [5, 6].

Levodopa is the most efficacious and well-tolerated drug for the treatment of patients with PD [7], though it has been shown to lead to increased serum homocysteine (hcy) levels [1]. This is due to the O-methylation of levodopa, which is catalyzed by the enzyme catechol-O-methyltransferase (COMT) and requires S-adenosylmethionine (SAM) as the methyl donor for the production of S-adenosylhomocysteine (SAH), which is rapidly hydrolyzed to hcy. This chronic increase in hcy synthesis exceeds the capacity of cells to metabolize hcy, leading to elevated serum hcy levels [8]. Serum hcy levels in patients with PD treated with levodopa are specifically thought to be elevated due to increased synthesis from the metabolism of levodopa by COMT [1, 4, 8]. A previous animal study demonstrated that pre-treatment with a COMT inhibitor can block the elevation of serum hcy levels when levodopa is given [9]. These findings suggest that a COMT inhibitor such as

entacapone may reduce levodopa-induced elevations in serum hcy levels in patients with PD. Despite these findings, it is unclear whether hyperhomocysteinemia in PD patients is related to cognitive decline. Furthermore, little work has been done to assess the effects of COMT inhibitors on dementia in PD patients.

Therefore, in this study we sought to determine whether COMT inhibitors were able to block elevations in serum hcy levels in PD patients, and consequently reduce the occurrence of dementia.

METHODS

This study was approved by the local ethics committee, and each patient gave written informed consent prior to participation. A series of consecutive patients were admitted to the Movement Disorder and Parkinson's Disease Unit of the Department of Neurology at the Catholic Medical Center of Korea between October 2010 and December 2011. Data from 73 PD patients (38 PD patients without dementia (PDwoD) and 35 PD patients with dementia [PDD]) who were recruited for this study were compared with that of 48 healthy controls. There were no significant differences in age and sex between healthy controls and PD patients.

To compare only the PDwoD and the PDD patients, those with a clinical dementia rate (CDR) score of 0.5 or 1 and a mini-mental status examination (MMSE) score below 24 points were eligible for the study. The control group did not have any history or symptoms of PD, memory impairment, or other cognitive impairment according to the results of a dementia screening questionnaire. Additionally, control subjects did not have a history of other neurological diseases such as head trauma, epilepsy, cerebrovascular disease, or brain surgery. All of the subjects were examined in the dementia clinic and the movement disorder clinic at Incheon St. Mary's Hospital. The evaluation procedure consisted of taking a detailed medical history, physical and neurological examinations, neuropsychological assessments, laboratory tests, and magnetic resonance imaging (MRI) of the brain. Information regarding history of medical and neurological problems was obtained from patients, family members, or other caregivers. All PDD and PD patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria for Parkinson's Disease and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revision (DSM-IVR) criteria for dementia [10]. For all PDD patients, the onset of Parkinson's disease preceded the development of dementia by at least 12 months. We excluded those patients who displayed markedly fluctuating cognition with pronounced variations in attention and alertness, had recurrent vivid hallucinations (suggested by the presence of diffuse Lewy body disease), were taking medications (e.g. anticholinergic agents) that have been reported to influence cognition and memory, had any signs of atypical parkinsonism, or fulfilled the DSM-IVR criteria for delirium or amnesic or depressive disorders [11]. PD patients did not have any history or symptoms of memory impairment or other cognitive dysfunction according to the dementia screening questionnaire, or any cerebrovascular lesions on neuroimaging. In addition to the above mentioned exclusion criteria, we excluded patients with secondary causes of parkinsonism (e.g. Wilson's disease, neuroleptic drug use, or psychiatric diseases) that could potentially compromise the safety of the study.

The lifetime dose and duration of levodopa use was determined for each patient by retrospective chart review and verified by retrospective patient reporting. Motor impairment severity in patients with PD was evaluated according to the staging system by Hoehn and Yahr (H & Y stage) [12]. Serum hcy levels were measured routinely in all patients and healthy controls. Fasting venous blood samples (8-10h fast) were collected from all subjects in tubes containing ethylenediaminetetraacetic acid. The samples were immediately separated by centrifugation at 3,000 rpm for 10 min. The separated sera were stored at -70°C until the laboratory evaluation. Laboratory data were collected by an examiner whom was blinded to clinical details and patient information.

All PD patients were additionally categorized into two groups including those treated with levodopa alone (group 1) or levodopa and a COMT inhibitor (group 2). All patients in group 2 took entacapone 600 mg/day from the time that PD was diagnosed.

Statistical analysis was performed using an SPSS software

package, version 17.0. Results are expressed as the mean ± standard deviation. Analysis of variance (ANOVA) with post-hoc testing was used to compare continuous variables in the two PD groups and the healthy controls. Independent t-tests were used to compare continuous variables between each group. Pearson's Chi-square analysis was used to compare categorical variables. To evaluate the influence of COMT-inhibitor use on the occurrence of dementia in patients with PD, we determined the odds ratio by using binary logistic regression analysis. P-values < 0.05 were considered to be statistically significant.

RESULTS

The demographic characteristics of all subjects are summarized in Table 1. There were no overall significant differences in age or gender distribution between PD patients and healthy controls, though PDD patients were significantly older than PDwoD patients and healthy controls. Additionally, the duration of disease and symptoms in the PDD versus PDwoD groups were significantly different, though there were no differences in daily levodopa doses between these groups. Serum hcy levels were greater in the PDD group than the PDwoD group, but there was no difference between the PDwoD and the healthy control subjects.

Regarding the effects of the COMT-inhibitor, no correlation was found between serum hcy levels in groups 1 and 2. In addition, there was no difference in the number of PDD patients between groups 1 and 2. Group 2 did, however, show a longer duration of treatment and greater severity of motor symptoms than group 1 (Table 2). Furthermore, binary logis-

Table 1. Baseline characteristics of all the subjects with PD and healthy controls

	PDwoD	PDD	HC	*p* value
Total Number of subjects	38	35	48	
Gender, male	16	13	11	0.163
Age (year)*	64.66 ± 7.64	72.46 ± 7.00	66.23 ± 11.83	0.001
Homocysteine level (μmol/L)*	11.46 ± 3.44	23.97 ± 24.93	12.52 ± 4.19	0.001
Vit. B12 (pg/mL)†	686.55 ± 323.69	658.22 ± 439.46	654.14 ± 257.24	0.84
Folate (ng/mL)†	15.21 ± 11.34	13.01 ± 12.01	17.01 ± 14.82	0.354
Duration of PD symptoms (month)	28.05 ± 11.96	43.78 ± 44.11	ND	0.006
Duration of PD treatment (month)	25.97 ± 14.71	41.51 ± 43.18	ND	0.008
Levodopa dose/day (mg)	442.71 ± 383.14	670.71 ± 31394	ND	0.486
MMSE‡	28.15 ± 1.18	20.57 ± 2.55	29.92 ± 0.91	0.001
CDR	0.35 ± 0.15	0.85 ± 0.33	ND	0.001
SOB	1.05 ± 0.42	4.252.42	ND	0.001
Hoehn & Yahr stage	1.96 ± 0.96	2.49 ± 0.84	ND	0.527

*Post-hoc comparison of Homocysteine level and age: HC = PDwoD < PDD; †Post-hoc comparison of Vit. B12 and folate : HC = PDwoD = PDD; ‡Post-hoc comparison of MMSE score:HC = PDwoD > PDD.
PD, Idiopathic Parkinson's disease; PDWoD, PD without dementia; PDD, PD with dementia; HC, Healthy control; ND, not done; MMSE, Mini-mental state examination; CDR, clinical dementia scale; SOB, sum of box of CDR.

Table 2. Comparison of characteristics among 2 subgroup in patients with PD and Healthy control group

	Group 1	Group 2	HC	*p* value
Total Number of subjects	42	31	48	
Age (year)*	70.02 ± 6.46	66.73 ± 9.74	66.23 ± 11.83	0.136
Homocysteine level (μmol/L)*	17.00 ± 12.34	18.59 ± 25.14	12.52 ± 4.19	0.162
Number of patient with dementia†	19	16	0	0.816
Duration of PD treatment (month)	25.58 ± 12.15	42.09 ± 45.08	ND	0.21
Duration of PD symptoms (month)	30.38 ± 11.64	41.29 ± 45.65	ND	0.15
Levodopa dose/day (mg)	538.82 ± 346.11	594.35 ± 385.66	ND	0.514
Hoehn & Yahr stage	1.99 ± 0.93	2.47 ± 0.87	ND	0.022

Value are expressed as mean ± standard deviation. Group 1: levdopa alone-treated PD patients, Group 2: levodopa plus COMT-inhibitor PD patients. *One-way Post-hoc comparison of Homocysteine level and age: Group 1 = Group 2 = Healthy control; †Pearson chi-square analysis was used.
PD, Idiopathic Parkinson's disease; HC, Healthy control; ND, not done.

tic regression analysis showed that the odds ratio for PDD with the use of a COMT-inhibitor was 0.864 (95% CI = 0.342-2.180).

DISCUSSION

It is well documented that older age, longer duration of disease, and greater severity of symptoms are associated with dementia in cases of advanced PD [4, 6, 13]. In this study, we also found that PDD is more strongly associated with older age and longer duration of disease than PDwoD. It has been proposed that elevated hcy levels in levodopa-treated PD may be caused by levodopa treatment rather than by the disease itself [2, 13]. Thus, elevated hcy has been identified as a risk factor for dementia. It is also known that elevated hcy levels lead to the acceleration of diseases such as atherosclerosis, neurodegeneration, and dementia [14], and that cerebrovascular diseases and cognitive impairment worsen the prognosis of patients with PD [4, 14]. Taken together, these studies suggest that elevated hcy levels in PD patients are correlated with cognitive impairment including dementia. Our data confirmed these findings, in that serum hcy levels in patients with PDD were higher than those with PDwoD. Furthermore, PDD patients had a longer duration of PD levodopa treatment than PDwoD patients.

While COMT-inhibitors are used currently in the treatment of PD, recent studies have also discussed the potential use of a COMT-inhibitor such as entacapone to decrease hcy concentrations [9, 15, 16]. This hypothesis is based on the idea that inhibition of peripheral COMT would not only improve the bioavailability of levodopa due to a decrease in peripheral degradation, but also lower the hcy levels [9,15]. Consequently, a lower hcy level could lead to improvement in cognitive impairment in PD patients. On the contrary, however, the present study showed no relationship between hcy levels and COMT-inhibitor use. Furthermore, we did not find any correlation between administration of a COMT-inhibitor and the occurrence of dementia in PD patients (odds ratio = 0.864, 95% CI = 0.342-2.180). Therefore we could cautiously assume that pretreatment with a COMT-inhibitor in PD patients did not prevent the effects of levodopa on hcy levels or the occurrence of dementia in PD patients.

In conclusion, our findings agree with previous studies in that levodopa treatment in PD patients results in elevated hcy concentrations. We also found, however, that a COMT-inhibitor did not prevent cognitive impairment in PD patients. Therefore, future large-scale longitudinal studies are needed to further clarify the effects of COMT-inhibitors on dementia and the relationship between COMT-inhibitors and hcy concentrations in patients with PD.

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