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The effect of levodopa benserazide hydrochloride on homocysteinemia levels in patients with Parkinson's disease and treatment of hyperhomocysteinemia

G. GUO, S. XU, L.-D. CAO, Q.-Y. WU

Department of Neurology, The First People's Hospital of Zhangjiagang, Zhangjiagang, China

Abstract. – OBJECTIVE: This study aims to investigate hyperhomocysteinemia (HHcy) resulted from treatment in patients with Parkinson's disease (PD) and to evaluate the therapeutic outcome of HHcy.

PATIENTS AND METHODS: Ninety-three newly diagnosed PD patients were divided into Madopar group (treated with Madopar) and non-Madopar group (not treated with Madopar). Plasma Hcy levels were measured. Five months later, 67 patients presenting with HHcy were randomly divided into treatment group (n = 34) (receiving methylcobalamin 500 μg, tid, and folic acid 50 mg, tid, orally) and control group (n = 33). Madopar dosage was maintained in both groups. MRI examination was performed to detect cerebral ischemia and patients were evaluated by Webster's rating scale. Plasma Hcy levels were measured at 3-month follow-up. Webster's scores and MRI were performed at 6-month follow-up.

RESULTS: At the initial visit, Hcy levels of patients of Madopar group were significantly higher than those of non-Madopar group (18.52 ± 6.48 μmol/L) *vs*. (15.78 ± 3.42), $p < 0.05$]. At 5-month follow-up, patients of the non-Madopar group presented significantly increased Hcy levels (18.97 ± 7.42 μmol/L) compare with pre-treatment Hcy levels ($p < 0.05$), whereas Hcy levels were slightly increased in patients of Madopar group (20.61 ± 7.87 μmol/L, $p > 0.05$). In the treatment group, serum Hcy levels were significantly decreased after 3-month treatment with methylcobalamin and folic acid ($p < 0.01$). However, serum Hcy levels were not significantly changed in patients of the control group. In addition, in the treatment group, no patient presented ischemic stroke with clinical symptoms and four patients were confirmed with new cerebral ischemic and lacunar lesions by MRI examination. However, in the control group, two ischemic strokes with clinical symptoms and 11 new cerebral ischemic and lacunar lesions were detected. Significant differences were observed between two groups ($p < 0.05$). Furthermore, post-treatment modified Webster scores were significantly decreased than pre-treatment scores for both groups. However, no significant differences were found between groups ($p > 0.05$).

CONCLUSIONS: Oral administration of Levodopa in the treatment of PD can cause HHcy, which can result in increased occurrence of ischemic stroke. Supplementation of methylcobalamin and folic acid can effectively reduce Hcy level and thereby prevent the occurrence of ischemic stroke.

Key Words:
Parkinson's disease, Levodopa, Hyperhomocysteine, Cerebral infarction.

Introduction

Levodopa/benserazide hydrochloride (Madopar) is the primary medication commonly used in the treatment of Parkinson's disease (PD). The administration of Levodopa can cause the increase in the plasma homocysteine (Hcy)[1]. A large number of studies have shown that hyperhomocysteinemia (HHcy) is an independent risk factor for cerebrovascular disease and the risk increases with the increasing concentration of Hcy[2]. In addition, some other evidence[3] has demonstrated that HHcy is associated with many neurodegenerative diseases. Therefore, the treatment of HHcy is of significant importance in the management of PD patients treated with Levodopa. In the present work, methylcobalamin and folic acid were used in the treatment of PD patients complicated by HHcy resulted from administration of Madopar. Results were compared with those of controls with same conditions.

Corresponding Author: Qiuyi Wu, MD; e-mail: qiuyi1028@sohu.com

Patients and Methods

Patients

Between June 2012 and June 2014, 93 patients with newly diagnosed PD (male 94, female 29, age range 49-76 years, mean age 62.47 ± 5.76 years) were enrolled in this study. All patients met the diagnostic criteria of PD developed by the Movement Disorders and PD Study Group of Chinese Society of Neurology in 2006[4]. Patients with acute or chronic liver and kidney dysfunction, thyroid disease, malignant tumor, various types of parkinsonism and those having taken vitamin B within two weeks were excluded from the study. For all these patients, the course of the disease lasted between six months to two years. Of these patients, 41 (male 30, female 11, age range 49-74 years, mean age of 61.86 ± 5.21 years) were not treated with (Non-Madopar group), while 52 (male 34, female 18, age range 51-76 years, mean age of 63.13 ± 4.12 years) were treated with Levodopa/Benserazide Hydrochloride (LBH) (Madopar group). No significant differences were observed in the age and gender between two groups of patients ($p > 0.05$). Among these patients, 67 PD patients who presented HHcy after five-month LBH treatment were included in this research. These patients were, then, randomly divided into treatment group (n = 34, male 25, female 9, age range of 51-76 years, mean age of 62.78 ± 4.23 years) and control group (n = 33, male 27, female 6, age range of 53-74 years, mean age of 61.51 ± 5.33 years). No significant differences were observed in the age and gender between two groups ($p > 0.05$).

Methods

Patients were started on Madopar (125 mg twice a day) and the dosage was adjusted and maintained after PD symptoms were improved. Morning fasting blood samples were collected both at the initial hospital visit and five months after treatment for the measurement of serum Hcy levels (reference value 5-15 μmol/L). Patients with Hcy level > 15 μmol/L were diagnosed with HHcy. Moreover, cranial MRI examination was performed to evaluate intracranial ischemia and cerebral infarction scored by Webster Rating Scale. Madopar was maintained in two groups of patients. Methylcobalamin (500 μg, tid) and folic acid (5 mg, qd) were administered orally in patients of treatment group. Serum Hcy levels were measured three months later. Webster scores were evaluated at six-month follow-up and MRI examination was performed again to detect any new onset of cerebral ischemia and infarction.

Statistical Analysis

Modified Webster's scale was used to compare pre-treatment and post-treatment conditions. Statistic analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± SD and were analyzed using *t*-test. Qualitative data were analyzed using chi-squared test (χ^2). $p < 0.05$ was considered statistically significant.

Results

Hcy Levels at Initial Visit and 5-Month Follow-Up

At the initial visit, Hcy levels of patients of Madopar group were significantly higher than those of non-Madopar group [(18.52 ± 6.48 μmol/L) *vs.* (15.78 ± 3.42 μmol/L), $p < 0.05$]. At 5-month follow-up, patients of the non-Madopar group presented significantly increased Hcy levels (18.97 ± 7.42 μmol/L) compare with pre-treatment Hcy levels ($p < 0.05$), whereas Hcy levels were slightly increased in patients of Madopar group (20.61 ± 7.87 μmol/L, $p > 0.05$) (Table I).

Pre-treatment and Post-Treatment Serum Hcy Levels ($\bar{x}$ ± s) and Occurrence of Ischemic Cerebral Stroke

In the treatment group, serum Hcy levels were significantly decreased after 3-month treatment with methylcobalamin and folic acid ($p < 0.01$).

Table I. Serum Hcy levels at initial visit and 5-month follow-up ($\bar{x}$ ± s).

n	Serum Hcy at initial visit (umol/L)	Serum Hcy at follow-up (umol/L)
Non-madopar group 41	15.78 ± 3.42	18.97 ± 7.42
Madopar group 52	18.52 ± 6.48	20.61 ± 7.87

Table II. Pre-treatment and post-treatment serum Hcy levels ($\bar{x} \pm s$) and occurrence of ischemic cerebral stroke. The values of Hcy are expressed as μmol/L.

n	Pre-treatment Hcy levels	Post-treatment Hcy levels	occurrence of ischemic stroke
Treatment group 34	24.78 ± 4.72	11.93 ± 5.61	11.76%
Control group 33	23.45 ± 6.23	24.14 ± 7.46	39.39%

However, serum Hcy levels were not significantly changed in patients of the control group. In addition, in the treatment group, one patient presented ischemic stroke with clinical symptoms and four patients were confirmed with new cerebral ischemic and lacunar lesions by MRI examination. However, in the control group, ischemic stroke with clinical symptoms occurred in two patients and new cerebral ischemic and lacunar lesions were detected in 11 patients. Significant differences were observed between two groups ($p < 0.05$). Furthermore, post-treatment modified Webster scores were significantly decreased than pre-treatment scores for both groups. However, no significant differences were found between groups ($p > 0.05$) (Tables II, III).

Discussion

Currently, combined preparation of is the most widely used treatment of PD. Certain study[5] has shown that prolonged administration of results in HHcy and hypertrophy of the intima-media complex (IMC) of the carotid artery, and HHcy is associated with IMC hypertrophy. During Madopar treatment, Levodopa is decarboxylated by dopa decarboxylase to generate dopamine, which is then transformed to 3-oxo-methyl dopamine via methylation by Catechol-O-methyltransferase (COMT). In addition, S-adenosylmethionine, the methyl group provider, is demethylated to produce S-adenosyl-Hcy, which is further deadenylated to generate Hcy. Therefore, long-term therapy with Levodopa requires more methyl group supply form S-adenosylmethionine and, thereby, leads to HHcy. The present study showed that Hcy levels at initial visit were significantly higher in patients of the Madopar group than in the non-Madopar group, while serum Hcy levels were significantly increased in patients of the non-Madopar group after 5-month treatment with Madopar. Hence, oral administration of Madopar can cause a significant increase in serum Hcy level in PD patients, which is consistent with the results of other studies[6-8].

Numerous clinical reports have shown that HHcy is closely associated with the occurrence of cerebrovascular disease. HHcy is an important and independent risk factor for atherosclerosis and the mechanisms by which HHcy causes atherosclerosis and thrombosis have been reported in a few studies[9,10]. Moller et al[11] demonstrated that patients with HHcy are at higher risk (3.97 times) for cerebrovascular disease than patients with normal Hcy levels. In the present study, Hcy levels were significantly decreased after treatment with methylcobalamin and folic acid in some PD patients with HHcy after LBH therapy ($p < 0.01$). Besides, these patients experienced significantly less ischemic stroke attack ($p < 0.05$). However, no significant differences were found in Webster's scores between two groups.

Conclusions

In brief, oral administration of LBH in the treatment of PD can cause HHcy, which can result in increased prevalence of ischemic stroke. Supplementation of methylcobalamin and folic acid can effectively reduce Hcy level and, thereby, prevent the occurrence of ischemic stroke. Therefore, routine monitoring plasma Hcy in PD

Table III. Pre-treatment and post-treatment Webster's scores ($\bar{x} \pm s$).

n	Pre-treatment scores	Post-treatment scores
Treatment group 34	11.37 ± 3.43	11.58 ± 4.15
Control group 33	12.19 ± 5.24	11.86 ± 4.47

patients receiving LBH treatment is essential to detect an aberrant increase in Hcy and to allow for immediate intervention. However, due to fewer patients included in this study and shorter follow-up duration, the conclusion of this study cannot be applied to the general population. To this end, a bigger sample size and longer follow-up duration are required for further studies to obtain more scientific and rational conclusion to guide PD treatment in clinical practice.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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