Short communication

The effect of levodopa treatment on cerebral hemodynamics in patients with Parkinson’s disease: Serial transcranial Doppler studies

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Levodopa treatment in patients with Parkinson’s disease (PD) is known to cause elevation in serum homocysteine levels. We investigated whether this increase in homocysteine level influences cerebral vascular flow velocity and resistance using transcranial Doppler (TCD). This study included 17 patients with de novo PD. Homocysteine levels and TCD parameters at middle cerebral artery were investigated before and after 3 months of levodopa treatment. Correlation analyses were done between changes in homocysteine levels and TCD parameters. After 3 months of levodopa treatment, homocysteine level increased significantly from 13.3 mg/dL to 17.0 mg/dL (p < 0.001), but there were no meaningful changes in mean velocity (MV) and pulsatility index (PI). Correlation analysis revealed that the changes in homocysteine level had negative correlation with MV (r = −0.53, p = 0.027) and positive correlation with PI (r = 0.55, p = 0.028). Our study infer that although short-term treatment of levodopa itself does not cause overall alteration of cerebral blood flow velocities and resistances, patients who has greater degree of increased homocysteine level may still be at a risk of developing cerebral vascular stiffness.

1. Introduction

Levodopa treatment is the gold standard therapy in patients with Parkinson’s disease (PD), with its unequivocal effect on controlling motor symptoms, improving quality of life, and prolonging patient’s life-expectancy. Levodopa therapy does, however, cause increase in serum homocysteine level as the drug is metabolized via catechol O-methyltransferase, and high level of serum homocysteine is known to be an independent risk factor for vascular diseases and cognitive impairments in elderly people.[1]. Indeed, some reports have demonstrated that elevated homocysteine levels in PD patients might be associated with increased prevalence of coronary artery disease, hypertrophy of carotid artery, and peripheral neurodegeneration [2–4], albeit there is no clear evidence that this is related to increased stroke risk in PD patients [5,6].

Homocysteine is known to cause endothelial dysfunction-mediated vascular impairment, but there have never been any studies on the effect of hyperhomocysteinemia on cerebral hemodynamics in PD patients treated with levodopa. In this study, we prospectively evaluated the changes of transcranial Doppler (TCD) parameters in de novo PD patients after 3 months of levodopa treatment and performed a correlation analysis between changes in each TCD parameter and changes in homocysteine levels.

2. Patients and methods

We prospectively enrolled 22 de novo PD patients from Mar 2007 to Feb 2008. PD was diagnosed according to the United Kingdom PD Society Brain Bank Clinical Diagnosis Criteria [7]. We evaluated TCD parameters and total plasma homocysteine concentration at baseline and 3 months after levodopa/carbidopa administration with maintenance dose of 450/75 mg/d. All the patients gave informed consent for their participation. Study protocol was reviewed and approval was waivered by ethics board of Ajou University Hospital.

All TCD studies were performed by a single operator with a three-dimensional mapping instrument (Trans-scan, EME) using examination techniques similar to those previously described [8]. Doppler signals from the left main stem of the middle cerebral artery (MCA) were obtained with a 2-MHz probe attached to a stereotactic headpiece through a transtemporal window at a depth of 62–66 mm, and follow-up TCD in each patient was performed at the same depth to initial examination. Total homocysteine concentration was measured from blood samples at baseline and follow-up, which were collected in a fasting state and were carried out in the mornings.

The Wilcoxon signed rank test was used to assess significant change of TCD parameters and homocysteine levels. Spearman correlation analysis was used to assess the significance of the relationship between the change of TCD parameters and changes of homocysteine levels. A level of p < 0.05 was regarded as statistically significant.

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3. Results

Of 22 patients with PD initially studied, 5 patients were excluded because of lack of TCD data due to poor temporal windows. The details of demographic characteristics of 17 patients at baseline and the changes of TCD parameters at follow-up are summarized in Table 1.

Compared to baseline, there was a significant increase of homocysteine levels after 3 months of levodopa treatment (13.3 vs 17.0 mg/dl; \( p < 0.001 \)). In comparison of changes in TCD parameters after levodopa treatment, there was no significant difference of mean velocity (MV) at proximal MCA (48.6 vs 48.4 cm/s; \( p > 0.05 \)) nor pulsatility index (PI) value (0.89 vs 0.92; \( p > 0.05 \)) between baseline and 3 months after levodopa treatment.

On correlation analysis of age and TCD parameters, age showed significantly positive correlation with baseline PI (\( r = 0.51, p = 0.037 \)). Correlation analysis between changes in homocysteine levels and TCD parameters showed that the change in the MV had a significantly negative correlation with the change in homocysteine levels (\( r = -0.53, p = 0.027 \), Fig. 1A). After adjusting age due to its influence on PI, the PI also showed significantly positive correlation with the change in homocysteine level (\( r = 0.55, p = 0.028 \), Fig. 1B).

4. Discussion

Our study demonstrated that although short-term treatment of levodopa in PD patients significantly increased the serum homocysteine level, there were no significant changes in MV and PI at serial TCD. However, the change of homocysteine levels showed a significant negative correlation with changes in MV and a significant positive correlation with changes in PI values.

Several lines of evidences have suggested that hyperhomocysteinemia can induce endothelial dysfunction, smooth muscle cell proliferation, and the alteration of the elastic properties of the vascular wall. Thus, hyperhomocysteinemia can lead to increase in systemic vascular resistance and result in increased vascular stiffness. Originally, the PI was designed to measure vascular resistance and this relationship was proved in the brachial arteries [9], suggesting the increased PI may represent enhanced cerebrovascular resistance in the cerebral circulation. Accordingly, a positive correlation between the changes of homocysteine levels and that of PI in this study may indicate that after levodopa treatment in PD, cerebrovascular resistance may increase proportionally to the increase in the homocysteine levels. This increased cerebrovascular resistance may decrease mean MCA velocity after levodopa treatment, thus resulting an inverse correlation between the change in homocysteine levels and that in the MCA velocities.

In this study, we did not find significant change in the MV and PI as a whole group even when there was significant increases in the homocysteine level. This is difficult to reconcile with previous report that changes in homocysteine level had significant effect on peripheral vascular reactivity [10]. However, this finding is in agreement with previous results of the change in cerebral blood flow velocities after a standardized methionine challenge. Rogan and colleagues reported that although homocysteine levels increased significantly after a methionine loading, no significant changes were observed in the resting cerebral flow velocities [11]. It is known that the cerebral vasculature differs in many functional and morphological aspects from the peripheral vasculature, having a wider compensatory range to maintain adequate blood flow than peripheral vasculature [11]. This compensatory capacity of cerebral vasculature may result in no gross alteration of cerebral blood flow velocities and PI even after increased serum homocysteine levels.

Some might argue that 3 months of homocysteine elevation would be too short to be causing any changes in vascular autoregulation. However, Manrique and colleagues has reported that after 3 months of homocysteine lowering therapy in patients who had renal transplantation, endothelial function was found to be enhanced [12]. Some might also argue that it is levodopa itself, not the elevated homocysteine level, that has brought out the changes in MV and PI observed in this study. Not much study has been done previously regarding the

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Table 1
Characteristics of patients at baseline and after 3 months of levodopa treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>3 month follow-up</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.9 ± 8.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex (female, %)</td>
<td>11 (45%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>1.6 ± 0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>2.1 ± 0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Homocysteine (mg/dL)</td>
<td>13.3 ± 4.5</td>
<td>17.0 ± 7.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MV (cm/s)</td>
<td>48.6 ± 7.7</td>
<td>48.4 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>PI</td>
<td>0.89 ± 0.22</td>
<td>0.92 ± 0.25</td>
<td>NS</td>
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</table>

MV, mean velocity; PI, pulsatility index.

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**Fig. 1.** Relationship between change in homocysteine levels and change in the MV (A), and between change in homocysteine levels and the PI (B), after 3 months of levodopa treatment. Spearman correlation analysis showed a significantly inverse correlation between change in homocysteine levels with change in the MV (\( r = -0.53, p = 0.027 \)). After adjusting for age, the PI also showed significantly positive correlation with the change in homocysteine level (\( r = 0.55, p = 0.028 \)).
effect of levodopa’s influence on hemodynamics, but one study has found that cerebral hemodynamic parameters were similar in patients with PD regardless of whether they were on- or off-levodopa state [13].

Therefore, our study infer that although short-term treatment of levodopa itself does not cause overall alteration of cerebral blood flow velocities and resistances, patients who have greater degree of increased homocysteine level may still be at a risk of developing cerebral vascular stiffness which may be caused by endothelial dysfunction. Further study is warranted with larger size and a control group in order to find out if this particular group of PD patients are more vulnerable to stroke and if they will benefit from homocysteine lowering therapies.

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