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Author(s)	Fukushima, Tetsuhito; Tan, Xiaodong; Luo, Yunwen; Wang, Puqing; Song, Jinhui; Kanda, Hideyuki; Hayakawa, Takehito; Kumagai, Tomohiro; Kakamu, Takeyasu; Tsuji, Masayoshi; Hidaka, Tomoo; Mori, Yayoi
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[Original Article]

## HEAVY METALS IN BLOOD AND URINE AND ITS RELATION TO DEPRESSIVE SYMPTOMS IN PARKINSON'S DISEASE PATIENTS

TETSUHITO FUKUSHIMA<sup>1</sup>, XIAODONG TAN<sup>2</sup>, YUNWEN LUO<sup>3</sup>, PUQING WANG<sup>3</sup>,  
JINHUI SONG<sup>3</sup>, HIDEYUKI KANDA<sup>1</sup>, TAKEHITO HAYAKAWA<sup>1</sup>,  
TOMOHIRO KUMAGAI<sup>1</sup>, TAKEYASU KAKAMU<sup>1</sup>, MASAYOSHI TSUJI<sup>1</sup>,  
TOMOO HIDAKA<sup>1</sup> and YAYOI MORI<sup>1</sup>

<sup>1</sup>Department of Hygiene & Preventive Medicine, Fukushima Medical University School of Medicine, Fukushima City, Japan, <sup>2</sup>School of Public Health, Wuhan University, Wuhan, China, <sup>3</sup>Xiangfan No. 1 Hospital, Xiangfan, China

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**Abstract : Objectives** Some heavy metals are suspected to be pathogenic to both Parkinson's disease (PD) and depression. Common background may exist in them. **Methods** Subjects comprised PD patients with depression, PD patients without depression and controls recruited from the outpatient clinic in China. Morning blood and urine samples were used to measure concentrations of metals and vitamins. **Results** Whole-blood manganese was significantly higher in the PD patients without depression than in both the PD patients with depression and the controls. Serum iron was significantly higher in the PD patients without depression than in the controls. Urine iron was also significantly higher in the PD patients without depression than in the controls. Serum copper was significantly lower in the PD patients with depression than in both the PD patients without depression and the controls. **Conclusions** Excessive intake of iron and accumulation of manganese seemed to be involved in the etiology of non-depressive PD.

**Key words :** Depression, Parkinson's disease, Heavy metals, Vitamins, Blood and urine levels

### INTRODUCTION

Some reports have revealed the role of heavy metals in human depression. Copper (Cu) appeared to be deficient in depression, but other heavy metals tended to accumulate excessively in the hair of the depressed patients<sup>1</sup>. Not men but women with low dietary or supplemental zinc (Zn) intake were more likely to have depressive symptoms<sup>2</sup>. Some vitamins, such as folate and vitamin B<sub>12</sub> (VB<sub>12</sub>) are crucial for methylation in the biosynthetic pathway of brain myelin and biogenic amine, and borderline or low red blood cell folate was present in one third of depressive patients<sup>3</sup>.

Manganese (Mn) poisoning is well known to result in parkinsonian symptoms<sup>4</sup>. Chronic expo-

sure to Mn produces a parkinsonian syndrome, particularly in miners, welders, and ferroalloy and battery manufacture workers. However a case of Mn-induced human parkinsonism was reported<sup>5</sup>, and excess accumulation of Mn in daily life was suspected to be involved in some cases diagnosed with idiopathic Parkinson's disease (PD). Idiopathic PD and parkinsonian syndrome caused by Mn poisoning are known to be undistinguishable in terms of symptoms, and we suspect that many patients who have accumulated Mn in the body in daily life are diagnosed with idiopathic PD, or some heavy metals are involved in the etiology of idiopathic PD. In our previous study<sup>6,7</sup>, the blood and urine levels of Mn, iron (Fe), Cu and Zn, and serum vitamin E (VE) and VB<sub>12</sub> in the PD patients and the controls in a general

population were measured. Excessive intake of Fe and Cu, accumulation of Mn, VE/Cu imbalance in intake, and VB<sub>12</sub> decrease by Zn deficiency in the body seemed to be involved in the etiology of PD.

Depression is common in PD and approximately 30–40% of PD patients have significant depressive disorders<sup>8</sup>. Lemke *et al.*<sup>9</sup> reported anxiety and depression as risk factors for development of PD, possibly being present many years before the appearance of motor symptoms. Bower *et al.*<sup>10</sup> studied the association of three personality traits related to neuroticism with the subsequent risk of PD using a historical cohort study. The study suggested that an anxious personality trait might predict an increased risk of PD developing many years later. Sanyal *et al.*<sup>11</sup> also reported that the multivariate analysis revealed that a previous history of depression was associated with increased risk of PD.

From these reports, common background may exist in the etiology of both PD and depression. In the present study, the blood and urine levels of Mn, Fe, Cu and Zn, and serum VE and VB<sub>12</sub> in the PD patients with depression, the PD patients without depression and the controls in the general population were compared, and the relations among them were discussed.

## METHODS

Subjects were same as the previous report<sup>6</sup> and comprised 82 PD patients (47 men, 35 women; mean ( $\pm$ standard deviation) age, 64.0 $\pm$ 9.4 years) who had been patients for <3 years and were recruited from the outpatient clinic of Xiangfan No. 1 People's Hospital in Hubei, China between 2006 and 2008, and sex- and age-matched ( $\pm$ 3 years) controls ( $n=82$ ; mean age, 63.7 $\pm$ 9.4 years) with no PD, but with symptoms such as headache and dizziness, who were recruited from the same outpatient clinic at the same time. PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank<sup>12</sup>. The depressive status was assessed simultaneously with the diagnosis of PD in the first medical examination by the trained neurologist in Xiangfan No. 1 People's Hospital. DSM-IV criteria<sup>13</sup> was used for the primary diagnosis of a depressive disorder. Major depression and dysthymia were our outcomes of interest. The severity of depression in patients was assessed by the criteria of the Hamilton Depression Rating Scale (HAM-D-17)<sup>14</sup>, and a score  $\geq 14$  was defined as "depression"<sup>15</sup>.

All the PD patients and all the controls were examined by neurologists from the clinic and underwent computed tomography inspection to exclude secondary causes of parkinsonism and morbidity unsuitable for controls. Informed consent was obtained from all the subjects in written form, and the study protocol was approved by the ethics boards of Xiangfan No. 1 People's Hospital (Hubei, China) and Fukushima Medical University (Fukushima, Japan).

For measurement of heavy metals in blood, the PD patients were divided into two groups, 24 PD patients with depression (11 men, 13 women; mean age = 63.0 $\pm$ 9.6 years) and 58 PD patients without depression (36 men, 22 women; mean age=64.3 $\pm$ 9.4 years). After exclusion of one control woman with depressive symptoms, the controls consisted of 47 men and 34 women (mean age=63.7 $\pm$ 9.4 years). Because of lacking data of urine, some subjects were excluded and the data for the remaining 19 PD patients with depression (9 men, 10 women; mean age=63.3 $\pm$ 10.2 years), 52 PD patients without depression (31 men, 21 women; mean age=63.9 $\pm$ 9.6 years) and 70 controls (41 men, 29 women; mean age, 63.4 $\pm$ 9.7 years) were used for the urine analyses.

Morning blood and urine samples were collected before breakfast and used to measure concentrations of Mn, Fe, Cu, Zn, VE and VB<sub>12</sub>. Serum and urine Fe, Cu and Zn were measured by inductively coupled plasma atomic emission spectrometry. Whole-blood and urine Mn were determined by atomic absorption spectrometry. Serum VB<sub>12</sub> was measured by microparticle enzyme immunoassay, and VE was by fluorometric method. The measurements were done in the Research Center of Wuhan University School of Medicine according to the standard protocol of Wuhan University for the laboratory data. The reference ranges for these values are quoted from websites<sup>16–18</sup>.

The SPSS statistical package was used. Differences in sex among groups were assessed using the  $\chi^2$  test for bivariate analysis. Means for age were analyzed using analysis of variance. Means for continuous values were analyzed using Tukey's test among the three groups.

## RESULTS

No differences were seen in sex and age among the three groups.

The levels of heavy metals in blood of the subjects are shown in Fig. 1. The mean levels of

whole-blood Mn and serum Fe, Cu, Zn in PD patients with depression were  $1.69 \pm 1.02$  mg/dl,  $1.77 \pm 0.76$   $\mu$ g/ml,  $0.90 \pm 0.26$   $\mu$ g/ml and  $1.02 \pm 0.43$   $\mu$ g/ml, respectively. Those in PD patients without depression were  $2.98 \pm 2.59$  mg/dl,  $2.10 \pm 0.84$   $\mu$ g/ml,  $1.06 \pm 0.31$   $\mu$ g/ml and  $1.15 \pm 0.47$   $\mu$ g/ml, respectively. Those in controls were  $1.68 \pm 0.68$  mg/dl,  $1.51 \pm 0.78$   $\mu$ g/ml,  $1.02 \pm 0.22$   $\mu$ g/ml and  $1.14 \pm 0.49$   $\mu$ g/ml, respectively. The reference ranges for these values are 0.75-1.41 mg/dl, 0.45-1.45  $\mu$ g/ml, 0.8-1.5  $\mu$ g/ml and 0.6-1.2  $\mu$ g/ml, respectively. Whole-blood Mn was significantly higher in the PD patients without depression than in both the PD patients with depression and the controls. Serum Fe was significantly higher in the PD patients without depression than in the controls. Serum Cu was significantly lower in the PD

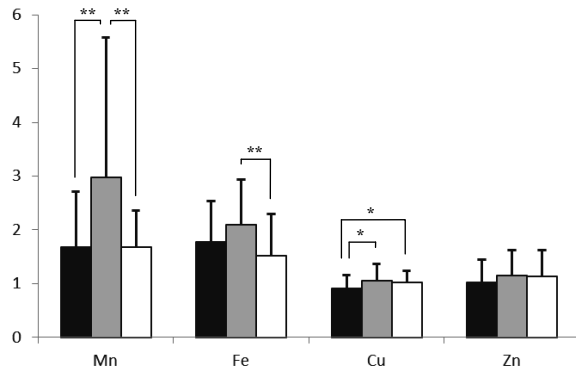


Fig. 1. Concentration of metals in blood. Each value is mean and standard deviation. Mn:  $\mu$ g/dl (whole blood), Fe, Cu, Zn:  $\mu$ g/ml (serum) ■, PD patients with depression; ■, PD patients without depression; □, Controls \* $p < 0.05$ , \*\* $p < 0.01$

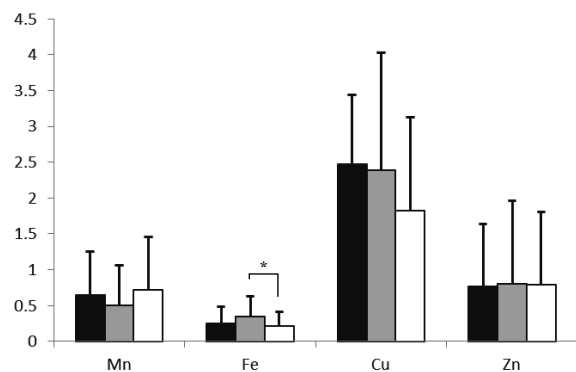


Fig. 2. Concentration of metals in urine. Each value is mean and standard deviation. Mn, Cu:  $\mu$ g/dl, Fe, Zn: mg/l ■, PD patients with depression; ■, PD patients without depression; □, Controls \* $p < 0.05$

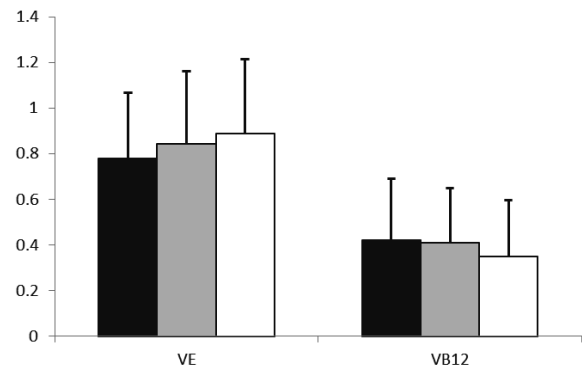


Fig. 3. The levels of serum vitamin E and serum vitamin B<sub>12</sub>. Each value is mean and standard deviation. VE: mg/dl, VB<sub>12</sub>: ng/ml ■, PD patients with depression; ■, PD patients without depression; □, Controls

patients with depression than in both the PD patients without depression and the controls.

The levels of heavy metals in urine of the subjects are shown in Fig. 2. The mean levels of Mn, Fe, Cu and Zn in PD patients with depression were  $0.65 \pm 0.68$   $\mu$ g/dl,  $0.25 \pm 0.23$  mg/l,  $2.47 \pm 0.96$   $\mu$ g/dl and  $0.77 \pm 0.87$  mg/l, respectively. Those in PD patients without depression were  $0.50 \pm 0.56$   $\mu$ g/dl,  $0.34 \pm 0.28$  mg/l,  $2.39 \pm 1.64$   $\mu$ g/dl and  $0.80 \pm 1.16$  mg/l, respectively. Those in controls were  $0.72 \pm 0.73$   $\mu$ g/dl,  $0.22 \pm 0.19$  mg/l,  $1.82 \pm 1.30$   $\mu$ g/dl and  $0.78 \pm 1.02$  mg/l, respectively. The reference ranges for these values are under 0.2  $\mu$ g/dl, 0.1-0.2 mg/day (0.066-0.2 mg/l, supposing urine volume per day is the range 1-1.5 liter), 1.4-6.3  $\mu$ g/dl, and 0.064-0.947 mg/l, respectively. Urine Fe was significantly higher in the PD patients without depression than in the controls.

The levels of serum VE and serum VB<sub>12</sub> of the subjects are shown in Fig. 3. The mean serum levels of VE and VB<sub>12</sub> in PD patients with depression were  $0.78 \pm 0.29$  mg/dl and  $0.42 \pm 0.27$  ng/ml, respectively. Those in PD patients without depression were  $0.84 \pm 0.32$  mg/dl and  $0.41 \pm 0.24$  ng/ml, respectively. Those in controls were  $0.89 \pm 0.33$  mg/dl and  $0.35 \pm 0.25$  ng/ml, respectively. The reference ranges for these values are 0.75-1.41 mg/dl and 0.233-0.914 ng/ml, respectively. There was no significant difference in the levels of serum VE and serum VB<sub>12</sub> among the three groups.

## DISCUSSION

Whole-blood Mn was significantly higher in the PD patients without depression than in both the PD patients with depression and the controls. Serum

Fe was significantly higher in the PD patients without depression than in the controls. Urine Fe was also significantly higher in the PD patients without depression than in the controls. Because in our previous study, positive correlations between whole-blood Mn and serum Fe concentrations were seen in both PD patients and controls in a general population in China, a route of simultaneous intake of Mn and Fe should exist<sup>6</sup>). From these results excessive intake of Fe and accumulation of Mn seemed to be involved in the etiology of non-depressive PD. Because low serum ferritin level was associated with depressive symptoms, Fe deficiency might commonly co-occur with depressive symptoms<sup>19</sup>). Although in our study mean serum Fe concentration in the PD patients with depression was higher than the upper limit of reference range and was not Fe deficiency level, Fe might have preventive effects on depression. However whole-blood Mn and serum Fe were not higher in the PD patients with depression than in the controls. Two types of PD, PD without depression which is affected by Mn and Fe and PD with depression which is not affected by them may possibly exist.

Gorell *et al.* found a significant association between PD and exposure to Cu in workers with more than 20 years of occupational exposure in a population-based case-control study in Detroit<sup>20</sup>). Cu-induced oxidative damage has been implicated in disorders associated with abnormal Cu metabolism and neurodegenerative changes<sup>21</sup>). In the present study serum Cu was significantly lower in the PD patients with depression than in both the PD patients without depression and the controls. Urine copper in both the PD patients with depression and the PD patients without depression was not significantly higher than that in the controls, but tended to be higher ( $p=0.175$  and  $p=0.075$ , respectively). It was suggested that excessive intake of Cu might be involved in the pathogenesis of PD, but serum Cu might be protective against depression of PD patients.

Antioxidant vitamins are expected to protect cells from oxidative damage and to prevent PD consequently<sup>22</sup>). VE may have neuroprotective effects against Fe-induced hippocampal and nigral neurotoxicity<sup>23</sup>). Higher intake of VE may be associated with decreasing risk of PD<sup>24,25</sup>). VE is generally believed to be protective against Cu-induced oxidative damage, too<sup>21</sup>). Meanwhile psychological stress reduced the plasma level of VE<sup>26</sup>) which was low in depression patients<sup>27</sup>). Depressive symptoms were associated with insufficient VE intake in

elderly people<sup>28</sup>). In the present study there was no significant difference in the levels of serum VE and serum VB<sub>12</sub> among the three groups. Further study is needed to verify the meaning of VE and VB<sub>12</sub> changes in blood on the etiology of PD and depression.

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