Original Article

Assessing of plasma levels of iron, zinc and copper in Iranian Parkinson's disease

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Abstract

Background: Trace elements have long been suspected to be involved in Parkinson's disease (PD) pathogenesis, but their exact roles have been remained controversial. In this study, we assessed the levels of copper (Cu), iron (Fe) and zinc (Zn) in different stage of PD patients.

Materials and Methods: Serum concentrations of iron, copper and zinc were measured in 109 patients with PD by colorimetric methods. Staging of the disease was evaluated according to Hoehn and Yahr (H and Y) and Unified PD Rating Scale III (UPDRS).

Results: Severity values of PD measured by UPRDSIII and HY stages with mean ± SD were 22.9 ± 1.81 and 1.8 ± 1.1, respectively. Mean ± SD values of iron, zinc and copper are 100.7 ± 289.2, 68.3 ± 5.32, and 196.8 ± 162.1 μg/dl, respectively. Serum iron level in most of the patients was normal (76.6%). Whereas zinc concentration in most participants was below the normal range (64.5%) and serum Cu in the majority of patients had a high normal concentration (42.7%) and did not significantly differ among various PD stages.

Conclusion: The result of this study does not confirm strong correlation between PD stages and serum levels of tested trace elements. The actual correlations between these elements and PD and whether modulating of these agents levels could be an effective approach in the treatment of this disease remain to be elucidated.

Key words: Copper, iron, Parkinson disease, plasma level, zinc

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INTRODUCTION

Parkinson's disease (PD) is a degenerative disorder of the nervous system characterized by impaired motor function, including resting tremors, bradykinesia, rigidity and postural instability. This disorder is manifested by a number of pathological events such as progressive death of dopaminergic neurons within the substantia nigra and accumulation of Lewy bodies. The pathogenesis of disease seems to be multi-factorial and both genetic and environmental agents have been supposed to play important role in this disease. Disturbances in trace elements homeostasis, oxidative stress[1] and mitochondrial dysfunctions have frequently been proposed to mediate or trigger this disease, but the evidences are not strongly convincing and constant.

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Trace elements, notably, zinc (Zn), iron (Fe) and copper (Cu), execute crucial and multiple roles in central nervous system (CNS) and are essential for CNS development and proper function. These metals are co-factors for a large number of different enzymes and may have other roles such as neuro-medulatory and pro- or anti-oxidant activity. Accumulating evidences suggest an association between altered concentrations of these metals with the risk of PD, and even modulation of their concentrations within the brain is emerging as a new therapeutic approach for PD.[2] In the onset and/or progress of neurodegenerative diseases, it have been thought that some metal such as Cu, Zn, and Fe for AD, Fe for PD, and Cu and Zn for familial ALS to be associated.[3]

Excessive iron accumulation and abnormalities in iron-binding protein has been observed in brain of patients with PD.[4] Iron as well as copper are redox active metals, and their accumulation in brain could lead to oxidative stress. It has been proposed that iron can induce aggregation of the alpha-synuclein protein, which is a major structural component of Lewy body fibrils.[4]

Copper has been proposed to be a risk factor and even a marker of PD.[5] This pro-oxidant element has been observed to enhance amyloid formation of alpha-synuclein.[6] Cu level has been reported to both increase in cerebrospinal fluid[7] and reduce in serum[8] during PD progression.

Zinc is also a known neuromodulator in CNS and also has anti-oxidants properties.[9] All increase,[10,11] no change[5] or decrease[12-15] in blood zinc concentration have been reported in PD.

The aim of this study was to compare the levels of Cu, Zn and Fe in various PD stages and assess their correlation with the severity of PD.

MATERIALS AND METHODS

Study design

This cross-sectional study was carried out at the Alzahra Hospital in Isfahan, Iran, as a double-blind study of determination of heavy metals in patients with PD. A total of 125 patients with PD, diagnosed by experienced neurologists, were eligible in criteria and asked to participate during September to November 2011. This study was conducted in the outpatient clinics and clinical wards. Patients were excluded if they were already taking iron or zinc supplements or were considered to have familial or early onset of PD (<40 years old). Finally, 109 patients had pertinent eligibility for our study. The diagnosis of PD was based on diagnostic criteria for PD including the presence of resting tremor, bradykinesia, and/or muscle rigidity. Disease duration (months) was defined as the period of time between diagnosis of PD and the clinical assessment for entry into this study. At baseline, we evaluated Hoehn and Yahr (HY) in four stages of 1–1.5, 2–2.5, 3, and 4–5[16] and also motor part of the Unified Parkinson's Disease Rating Scale III (UPDRS III).[17] All patients received standard protocol treatment for PD and provided written informed consent. The study protocol was reviewed and approved by the ethics in Research Committee, Isfahan University of Medical Sciences.

Laboratory analysis

Blood samples were obtained from patients after an overnight fasting. Serum concentrations of Fe, Cu and Zn were measured on a Hitachi 902 biochemistry analyzer by commercial colorimetric kits. Iron, zinc and copper level were within reference intervals 30–147, 70–150 and 70–140 μg/dl, respectively.

Statistical analysis

The effects of Fe, Zn, Cu (trace elements) on the stages of HY were evaluated using order logistic regression controlling the variables such as age, gender, disease duration. Associations between UPDRS Part III and trace elements were assessed using multiple linear regression models adjustment with age, gender, disease duration. SPSS statistical software version 18 was utilized for all statistical calculations. A P value of less than 0.05 was considered to be significant.

RESULTS

A total of 109 patients agreed to participate in this study. Mean ± SD values of age and disease duration were 61.4 ± 1.19 years and 57.2 ± 4.94 months, respectively. Severity values of PD measured by UPRDSIII and HY stages with mean ± SD were 22.9 ± 1.81 and 1.8 ± 1.1, respectively. Mean ± SD values of iron, zinc and copper are 100.7 ± 289.2, 68.3 ± 5.32, and 196.8 ± 162.1, respectively. Serum iron level in most of the patients was normal (76.6%). However, zinc concentration in most participants was below the normal range (64.5%). The contradictory result was shown about serum Cu level so the majority of patients had a high normal concentration (42.7%). Most participants were males 70.6% and 29.4% were females. Variants of the study population were divided into four groups based on HY staging, as shown in Table 1. Initial analysis showed that patients with higher HY stage were older (P value = 0.026). Iron, zinc and copper levels did not differ significantly between HY stages (Figures 1–3, respectively). When the severity of PD was evaluated by UPDRS III, only

there were significant associations between age and UPDRS (III) (*P* value = 0.024) [Table 1].

DISCUSSION

The relation between trace elements and PD risk and severity has been the subject of a limited number of previous studies, but the results have been non-consistent and controversial. As the results of this study indicates, serum concentrations of Cu, iron and Zn in PD do not significant correlates with disease progression. These results are similar to part of the previous publications[7,18] but do not confirm some others.[19,20] The real cause of these discrepancies among various studies is not clear.

This result does not completely rule out the possible etiological correlations between trace elements. Serum concentrations of these elements may not perfectly reflect their actual status in CNS, especially, in exact regions where Parkinson pathogenesis occurs. In contrast, based on reports about the accumulation of iron in brain of PD patients,[21-23] information about Fe level in plasma/serum of PD patients is more confounded, which changes in all respects from a decrease[19,24] to without change,[12,25,26] and to a raise[20] has been presented. In the present study, we found plasma Fe level was more elevated in higher steps in patients compared than early stages and dissimilarity with previous reports that could be explained by recruiting limited sample size in higher stages of disease progression. It seems that increase of plasma Fe in PD induced elevating Fe deposit in substantia nigra and then contributing to the progression of PD consequently potential correlation between increased Fe level and provoked risk for PD has been shown.[27]

Although in our study, Cu level in most of the PD patients was high (42.7%), literature on serum Cu in PD is conflicting. In one study, the levels of Cu and Zn in CSF were significantly higher and the level of Mn was also higher than those in the controls. Chronic occupational exposure to Mn or Cu is correlated with PD.[28] Hegde *et al*. in 2004[12] reported an increase of serum Cu levels without any correlation with disease severity in PD. In addition, Pall *et al*.,[29] an increscent of the Cu level in the cerebrospinal fluid of PD patients has been explained but this increase was not confirmed by other studies,[12] as reduction of this element also reported before especially in older PD patients.

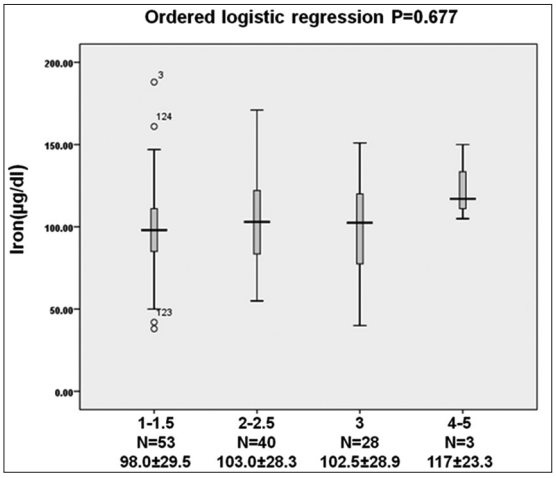

Figure 1: Serum Iron levels across Hoehn and Yahr stages. Associations between Hoehn and Yahr stages 1 to 4 and Iron levels were assessed using ordered logistic regression after multivariate adjustment for age, gender, disease duration

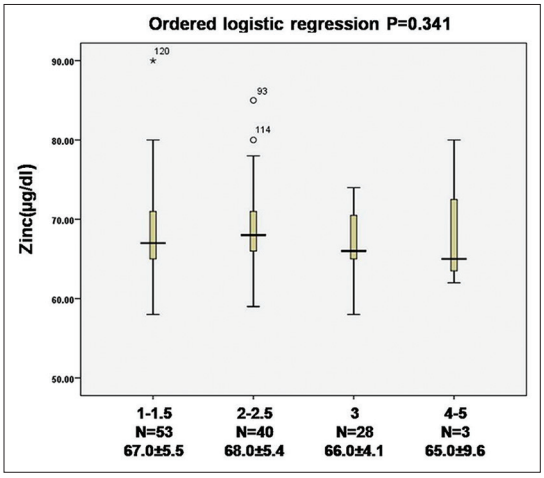

Figure 2: Serum Zinc levels across Hoehn and Yahr stages. Associations between Hoehn and Yahr stages 1 to 4 and Zinc levels were assessed using ordered logistic regression after multivariate adjustment for age, gender, disease duration

Table 1: Summery results of multiple linear regression model to UPDRS III and H and Y

Variables	UPDRS III		H and Y	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Age (years)	0.36 (0.05, 0.67)	0.024	0.036 (0.004, 0.06)	0.026
Sex (M/F)	−5.9 (−14.2, 2.4)	0. 16	0.22 (−0.61, 1.05)	0.66
Disease duration (months)	0.05 (−0.26, 0.13)	0.19	0.004 (0.003, 0.012)	0.26
Cu (µg/dl)	−0.005 (−0.028, 0.019)	0.68	0.001 (−0.002, 0.003)	0.54
Fe (µg/dl)	−0.01 (−0.14, 0.13)	0.89	0.002 (−0.01, 0.16)	0.67
Zn (µg/dl)	−0.26 (−0.95, 0.42)	0.44	0.39 (−0.11,0.032)	0.34

UPDRSIII: Unified Parkinson's disease rating stage part III motor, HY: Hoehn and Yahr, CI: Confidence interval

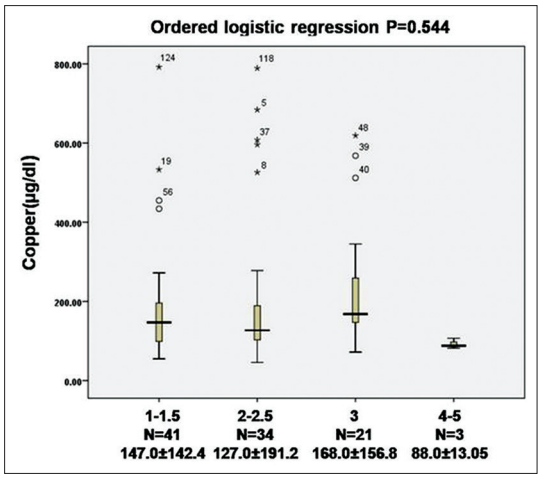

Figure 3: Serum Cu levels across Hoehn and Yahr stages. Associations between Hoehn and Yahr stages 1 to 4 and Cu levels were assessed using ordered logistic regression after multivariate adjustment for age, gender, disease duration

Indeed it seems that Cu change level may merely be a consequence or cause of PD.[27] Despite the diversity of information, recently Mariani *et al*. indicated a meta analysis which presented no difference in plasma/serum Cu and Fe in PD patients.[30]

On the other hand, plasma Zn represents greatest reduction (64.5%) in plasma level rather than other trace elements in our PD patients. Previously reported in small populations, diminishing of Zn by 27.1% and 23.1% in plasma/serum of PD patients has been[19,31] presented, whereas a few other studies showed no change of plasma/serum Zn level.[12,20,32] This difference could be explained by population variation and high biological variability in fluids. Contrary to our results, previous studies reported that lower plasma Zn level was associated with improved risk for PD[27,32] suggesting that in PD treatment, Zn addition might be advantageous. For determination of the role of Zn in the progression and treatment of PD disorder, considering the fact that it regulates response of both excitatory and inhibitory receptor in the CNS,[33] many investigations must be designed for better clarification.

In addition, distribution of these elements may also be influenced by confounding factors such as age, gender, race, PD-induced changes in life style and anti-Parkinson therapy.[34] It seems that the PD could induce changes in trace elements homeostasis rather than these elements acting as causative factor in PD.[35] The actual correlations between these elements and Parkinson disease and whether modulating of these agents levels could be a effective approach in the treatment of this disease remains to be elucidated. New candidates for the treatment of neurodegenerative diseases such as Cu-chelating agents,[36] Zn-chelating agents,[37] and, moreover, metallothioneins, which maintain Zn and Cu homeostasis,[38] have been suggested.

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