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Research report

Lower hemoglobin levels in patients with parkinson's disease are associated with disease severity and iron metabolism

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ABSTRACT

Although several lines of evidence suggest that low levels of hemoglobin are a risk factor for Parkinson's disease (PD), few studies have examined changes in hemoglobin after PD onset. In this study, we quantify alterations in hemoglobin after the onset of PD and explore possible mechanisms for changes in hemoglobin. We enrolled 213 PD and 219 control subjects between 2013 and 2014 at the Third Affiliated Hospital of Sun Yat-sen University and Nanfang Hospital of Southern Medical University. We collected data from routine blood tests (including markers of iron metabolism) and measured basic clinical parameters. The hemoglobin levels were lower in PD patients relative to control subjects (125.1 ± 15.68 g/L and 139.9 ± 11.83 g/L, respectively; $p < 0.001$). Serum iron levels did not change in PD patients compared to control subjects (14.92 ± 4.88 μmol/L and 15.73 ± 4.40 μmol/L, respectively; p=0.35). Total iron binding capacity (TIBC) was also unaltered (PD group: 48.29 ± 9.13 μmol/L; control group: 49.74 ± 8.35 μmol/L; p=0.43). The level of ferritin in PD and control subjects was 174.07 ± 74.04 ng/mL and 191.82 ± 91.49 ng/mL (p=0.04), respectively. We further analyzed the relationship between iron metabolism and PD by stratifying the data by disease severity and found that late-stage PD patients have lower levels of iron, ferritin, and TIBC (14.36 ± 4.95 μmol/L, 162.24 ± 71.25 μmol/L and 46.84 ± 10.15 ng/mL) compared to age-matched controls. Significant correlations were observed between hemoglobin levels and iron metablism. Our results suggest that hemoglobin levels are lower in PD patients compared to controls and are associated with the severity of PD and iron metabolism.

1. Introduction

Parkinson's disease is the second most common neurodegenerative disease. Its manifestations primarily include resting tremor, rigidity, bradykinesia, postural instability, and nonmotor symptoms, such as olfactory impairment, depression, and constipation (Adler and Beach, 2016). In addition, biochemical changes are also associated with PD. Recent studies found that patients with lower hemoglobin (HBG) were more susceptible to PD and that lower HBG may be a risk factor for PD (Abbott et al., 2012; Savica et al., 2009). However, HGB changes in patients with PD after disease onset have not been studied systematically. So far, only a small sample-size study has examined alterations in HGB after the onset of PD and the possible mechanisms that cause those alterations (Madenci et al., 2012). This study found that HGB levels did not change in PD patients compared with controls (Madenci et al., 2012). Iron, an important metal ion bound to hemoglobin, accumulates in the substantia nigra of PD patients (Martin et al., 2008; Reimao et al., 2015). In additon, some studies suggest that systemic iron metabolism also changes in PD, but these findings remain controversial. (Costa-Mallen et al., 2015; Logroscino et al., 1997; Marder et al., 1998; Pichler et al., 2013). To date, most studies have observed changes in HGB and iron metabolism, but have not explored the relationship between these changes and the course of PD. Considering the close association between iron metabolism and HBG, we hypothesized that abnormal iron metabolism may influence HBG levels in patients with PD. Tracking the dynamic changes in iron metabolism and HGB throughout the course of PD will help us to better understand the roles of iron metabolism and HGB in the pathogenesis of PD and to develop new treatments for PD. Therefore, this study aimed to clarify how hemoglobin and iron metabolism change after the

Abbreviations: HCT, hematocrit; HGB, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemo; MCHC, mean corpuscular hemoglobin concentration; PD, Parkinson's disease; RBC, red blood cell count; TIBC, total iron binding capacity; H & Y, Hoehn and Yahr scores

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Table 1
Demographic features of the groups. p value between two groups was > 0.05 in terms of age and gender. However, the p value for anemia was < 0.01.

Variables	Control group	PD group
Number	219	213
Male	119 (54.3%)	114 (53.5%)
Female	100 (45.7%)	99 (46.5%)
Age (years)	63.12 ± 6.01	63.4 ± 10.52
Disease duration (years)	0	5.13 ± 3.79
Daily L-dopa dosage (mg)	0	241 ± 105.28
H & Y score	0	1.54 ± 0.5
Anemia (n%)	19 (8.68%)	92 (43.19%)

onset of PD, and the relationship between those changes.

2. Results

2.1. Patient Characteristics

The clinical parameters of the two patient groups (PD patients and healthy controls) are reported in Table 1. The number of patients in the two groups (N) was comparable. Every patient with PD underwent madopar therapy. In terms of age and gender, no statistically significant differences were found between the two groups. However, the percentage of patients with anemia in the two groups was significantly different; the PD group had a lower incidence of anemia.

2.2. Comparison of the indicators of anemia between PD patients and control subjects

Overall, HGB gradually decreased with age in PD patients and controls (Figs. 1D and F). Further analysis confirmed that PD patients and controls had significantly different red blood cell counts (RBC), hemoglobin (HGB) levels , and hematocrit (HCT) levels. The levels of RBC, HGB, and HCT in PD patients were distinctively lower compared to controls. However, there were no signficiant differences in mean cell volume (MCV), mean corpuscular hemoglobin (MCH), or mean corpuscular hemoglobin concentration (MCHC) between PD patients and controls. Furthermore, when the PD patient group was divided into early-stage and late-stage PD according to the Hoehn and Yahr (H & Y) grading standard (H & Y score 1–2.5=early PD, H & Y score 3–5=late PD; (Muilwijk et al., 2013), we also observed a signifancant decrease in RBC, HGB, and HCT between late-stage PD patents and age-matched controls (referred to as the “late control” group). MCV, MCH, and MCHC were not significantly different between the late control and the late-stage PD groups (Table 2, Figs. 2A and B). When separated by gender, both men and women with PD were significantly different from controls in terms of RBC, HGB, and HCT, but not MCV, MCH, or MCHC (Table 2, Figs. 2C and D).

2.3. Comparison of iron metabolism between PD patients and control subjects

To study the effect of PD on iron metabolism, we chose to measure ferritin, serum iron, and TIBC. Overall, PD patients had significantly lower ferritin level than controls (Table 3 Fig. 2A). Although serum iron and TIBC showed a downward trend in PD patients compared with the controls, these changes did not reach statistical significance (Table 1 and Fig. 2A). After stratifying the data by disease serivity, we found a significant difference in serum iron and TIBC between late-stage PD patients and late controls (Table 3 and Fig. 2B). However, after separating the data by gender, we found no significant differences in ferritin, serum iron, or TIBC between PD paitents and controls, either for women or men (Table 3, Figs. 2C and 2D).

2.4. Correlation between anemia indicators and PD disease course and iron metabolism

To identify the underlying causes of the changes in anemia index that we observed (especially HGB), we conducted a correlation test and linear regression. This revealed a statistically significant, inverse correlation between disease severity and RBC, HGB, HCT, MCH, MCHC, serum iron, ferritin, and TIBC. The same trend was found to exist between H & Y score and RBC, HGB, HCT, MCH, MCHC, serum iron, ferritin, and TIBC. However, further linear regression analysis showed that there was no causal relationship between MCV, MCH, MCHC, TIBC, and H & Y score or disease duration after adjusting for patient age (Table 4). We found relatively few correlations between measures of anemia and iron metabolism. Only ferritin was significantly correlated with HGB and HCT levels. Additionally, serum iron levels were correlated with RBC and MCV after age-adjustment. (Table 5 and Fig. 1).

3. Discussion and conclusions

In this study, we found that levels of RBC, HGB, and HCT were lower in PD patients than controls. However, we found no significant differences in MCH, MCHC, or MCV in PD patients. Further subgroup analysis, which analyzed these parameters with respect to disease severity and gender, produced similar results. Exception for ferritin, the parameters of iron metabolism, such as serum iron and TIBC, did not show differences between PD patients and controls. Meanwhile, subgroup analysis with respect to disease severity showed that serum iron and TIBC were lower in late-stage PD patients than late controls. This indicates that iron metabolism disorders in PD patients grow more severe throughout the course of disease.

When the data were divided based on gender, we found no significant differences between PD patients and controls, either for women or men, in terms of serum iron, TIBC, or ferritin. We speculate that dividing the data for subgroup analysis decreased the number of subjects (N) per group, which decreased the power of the statistical analysis, and resulted in a non-significant p-value. We also observed some significant correlations between anemia and iron metabolism. This indicates that iron metabolism disorders are a possible risk factor for anemia.

Our study showed that parameters related to anema are decreased in patients with PD. Additionally, we found that RBC, HGB, and HCT levels decreased with disease duration and disease severity. The correlation between PD and HGB has been investigated in many clinical studies, however these studies reached very different conclusions. Two retrospective studies confirmed that changes in hemoglobin are detectable before the onset of PD. Savica et. al. found that early-life HGB level in PD patients is consistently lower than controls, both before disease onset and across all ages (Savica et al., 2009). A recent study found that mitochondrial HGB levels in the cerebellum are decreased in females with PD. However, males with PD had no decrease in mitochondrial HGB (Shephard et al., 2016). In our study, we did not compare HGB levels between male PD patients and female PD patients, because we found gender differences in HGB in the control population. The observed changes in HGB in peripheral blood, and even mitochondria, imply that hemoglobin may be involved in the pathogenesis of PD. This raises the question: are low HGB levels a pathological outcome of PD or protective response against PD? Another study conducted by Petrovitch et al. confirmed that men with higher HGB had a greater chance of developing PD late in life. This study found that if Hb increased from < 14 to ≥ 16 g/dL, PD incidence increased 3.2-fold (a relative hazard of 3.2), but found no other blood count measures (including HCT) that were related to PD incidence. This result is contrary to our findings. In our study, the male patients with PD had lower RBC, HGB, and HCT levels than male controls. In contrast to the findings reported in our study, data from a previous