News Release

Title

Longitudinal analysis of premotor anthropometric and serological markers of Parkinson's disease

Key Points

- **Parkinson's disease (PD) is a neurodegenerative disorder caused by loss of dopaminergic neurons, and is characterized by motor signs including bradykinesia, rigidity, resting tremor, and reduced postural reflex**
- **More than 50% of dopaminergic neuron in the substantia nigra are lost at the onset of motor symptoms in PD.**
- **Prodromal symptoms, such as dysautonomia, REM sleep behavior disorder (RBD), and hyposmia, antecede the onset of motor of cognitive dysfunction by 10-20 years.**
- **Our current results showed a premotor blood pressure increase in female PD patients and premotor decreases in haematocrit, total cholesterol, and low-density lipoprotein cholesterol in the male PD patients.**
- **Our study revealed that anthropometric and serological changes occurred before the emergence of motor symptoms in PD.**
- **Health examination, in combination with other evaluation, may facilitate early detection of PD before the onset of motor symptoms.**

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine have revealed that the blood pressure, hematocrit, and serum cholesterol levels change before the onset of motor symptoms in PD patients. This work was published online in *Scientific Reports* on November 25 2020.

Parkinson's disease (PD) is a debilitating neurodegenerative disorder in which nonmotor symptoms, such as constipation and hyposmia, precede the onset of motor symptoms by 20 years. At the timing of motor symptom onset, more than 50% of dopaminergic neurons are lost. The aim of this study was to identify biomarkers at the premotor stage of PD. We assessed the differences in longitudinal changes in anthropometric and serological indices obtained from health check-up data before and after the onset of motor symptoms between male and female PD patients and healthy subjects. We enrolled 22 male and 23 female PD patients and 60 male and 60 female healthy controls. A mixed-effects model was used to estimate the trajectory of each clinical marker over the years before and after motor symptoms onset in the PD subjects, which were then compared with the trajectories of the healthy controls. The results showed a premotor blood pressure increase in female PD patients and premotor decreases in haematocrit, total cholesterol and low-density lipoprotein cholesterol in the male patients. Our results indicated that blood pressure, haematocrit and serum cholesterol levels are potential premotor markers of PD. Additionally, the

changes in anthropometric and serological indices before PD motor symptoms onset were sex specific.

Research Background

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The frequency of the disorder is relatively high at 1.3 cases per 10,0000 people < 45 years old, 3,100 per 10,0000 in those 75–85 years old and 4,300 per 10,0000 in those > 85 years old. PD is characterized by motor signs of bradykinesia, rigidity, resting tremor, and reduced postural reflex, as well as by nonmotor symptoms, including cognitive, neuropsychiatric, sleep, autonomic and sensory disturbances. Some nonmotor symptoms, such as constipation, rapid eye movement sleep behavior disorder (RBD), and hyposmia, are known as premotor/prodromal symptoms. Because these symptoms manifest decades before motor symptoms, the pathogenesis of PD is thought to emerge long before the onset of motor symptoms.

Initiation of neurodegenerative process before neurological symptoms is a common feature of neurodegenerative disorders including Alzheimer's disease, in which the deposition of amyloid beta precedes the onset of dementia by mora than 20 years. This is the reason why attempts to identify biological markers for the preclinical stages have received increased attention. However, little is known about the longitudinal changes in biomarkers at a premotor stage of PD.

The aim of the present study was to examine longitudinal changes in biochemical and anthropometric indices at the premotor stage of PD. To this end, we investigated changes before and after motor symptoms onset in PD patients by analyzing health check-up longitudinal data.

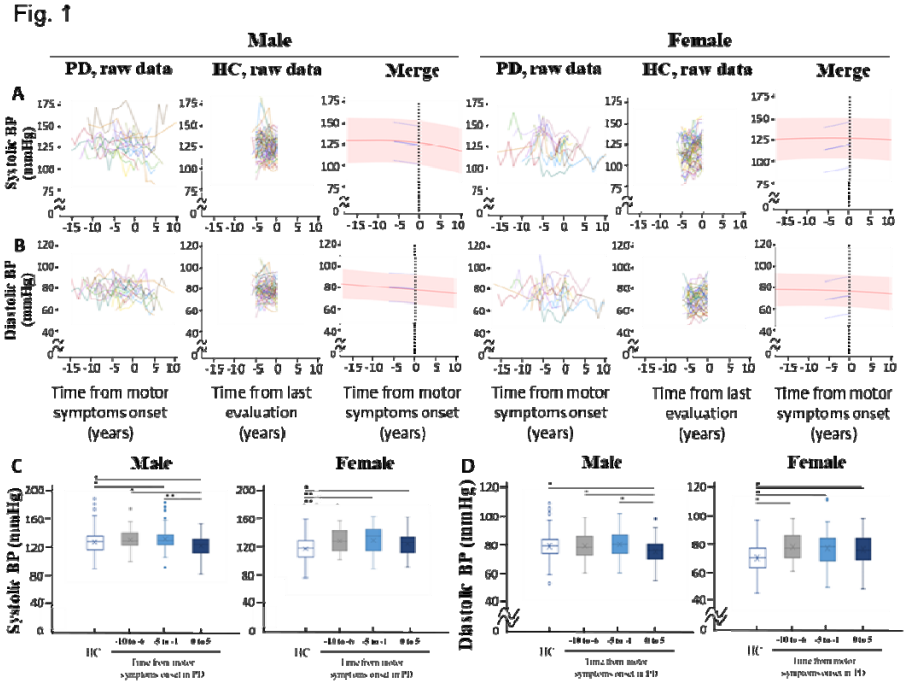
Research Results

We analyzed 45 PD patients (22 males and 23 females) whom health check-up data before the onset of motor symptoms were available, and 120 healthy controls (60 males and 60 females) whom health check-up data > 4 years from their last evaluation were available, and who did not have prodromal symptoms of PD (any of hyposmia, RBD and constipation).

First, we compared the baseline values of each item between the PD and healthy subjects for each sex separately. We defined the baseline as the onset of motor symptoms for PD groups and as the last evaluation for the healthy subjects. In males, there were significant differences between the PD patients and healthy controls in weight, body mass index (BMI), haematocrit (Ht), T-Cho, LDL-Cho and creatinine (Cr), and all the values of all these indices were lower in male PD patients than in the male healthy controls. In females, significant differences were found in height, systolic blood pressure (BP), diastolic BP, aspartate aminotransferase (AST) and T-Cho between the groups. The values of AST, systolic BP and diastolic BP were higher in female PD patients, whereas the values of other indices were lower in female PD patients than in the female healthy controls.

To detect premotor changes in indices, we analyzed the estimated trajectories of the factors that showed statistically significant differences at baseline between healthy subjects and those with PD for either sex: height, weight, BMI, systolic BP and diastolic BP. There was no premotor change in height and weight and BMI in either sex.

Fig. 1

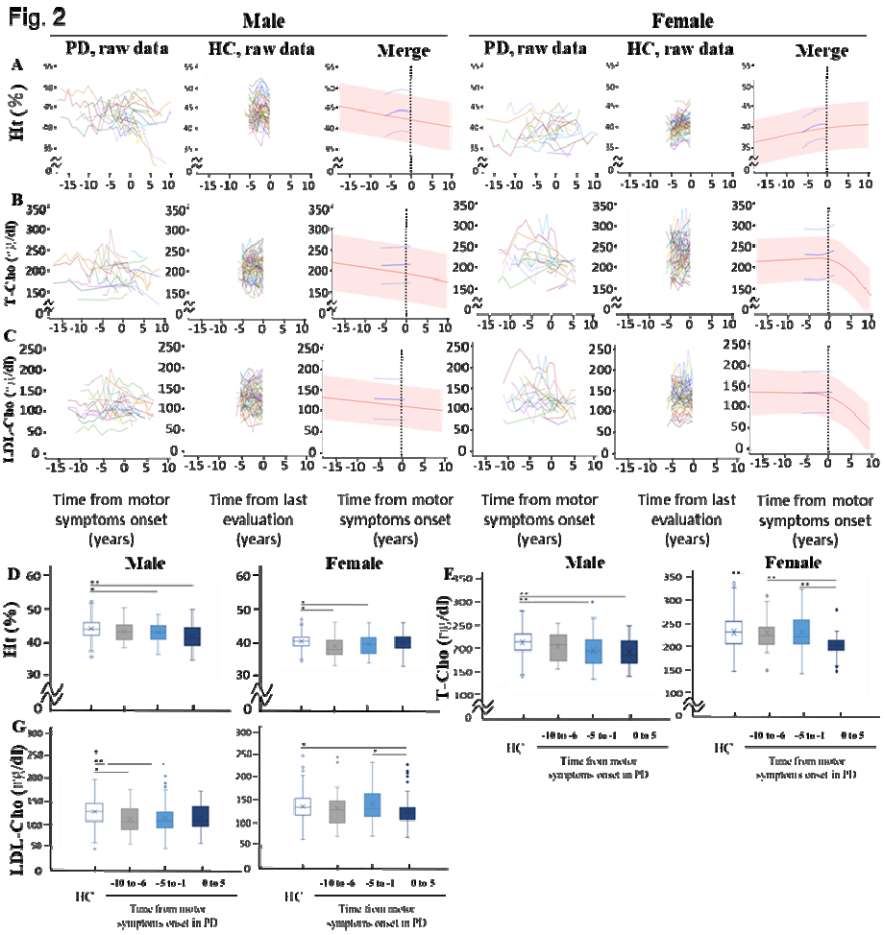


By contrast, the values of systolic and diastolic BP were elevated before motor onset in the female PD patients when compared with the female controls, and the difference decreased as the manifestation of motor symptoms increased, although these trends were not detected in males (Fig. 1A, D). To confirm the results of our linear mixed model analysis, we also directly compared the actual data of each item between the PD and healthy subjects for each PD disease stage (Fig. 1C, D). Increases in systolic and diastolic BP were observed >6 years before motor onset in the female PD patients, but the differences from the control values decreased with disease progression, as shown in the estimated trajectories.

Next, we analyzed the estimated trajectories of the blood examination items, which showed statistically significant differences at baseline between PD and healthy subjects for either sex: Ht, AST, T-Cho, LDL-Cho and Cr. In the male PD patients, the haematocrit values started to decrease before the onset of motor symptoms (Fig. 2A). The premotor changes of the serum values of AST and Cre were not observed in either sex. The T-Cho and LDL-Cho values began to decrease before the onset of motor symptoms in the male PD patients (Fig. 2B, C). These values showed progressive declines after the onset in both sexes, but a premotor change was not observed in the female PD patients. In the direct comparison of actual data, the haematocrit levels in the male PD patients showed a decrease from 5 years to 1 year before the motor onset (Fig. 2D). Serum T-Cho levels in the male PD subjects began to decrease 5 to 1 years before the onset of motor symptoms, whereas the values decreased only after motor onset in females (Fig. 2E). Similar results were obtained for the serum LDL-Cho levels (Fig. 3F).

Research Summary and Future Perspective

Our results showed a premotor blood pressure increase in female PD patients and premotor decreases in haematocrit, total cholesterol and low-density lipoprotein cholesterol in the male patients. Our results indicated that blood pressure, haematocrit and serum cholesterol levels are potential premotor markers of PD, and may be used with other examinations on premotor symptoms for early diagnosis of PD.



We are currently performing a prospective study on subjects at the prodromal phase of PD, and will start a clinical trial of neuroprotective therapy in such individuals.

Publication

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