Level of uric acid and uric acid/creatinine ratios in correlation with stage of Parkinson disease

Ling-Ling Zhong, PhDb, Ya-Qi Song, PhDb,c, Xiang-Yang Tian, PhDd,∗, Hua Cao, MDa, Ke-Ju Ju, MDd

Abstract
This study aims to investigate relationship between the level of uric acid (UA) and UA/creatinine ratios (UA/Cr) to the stage of Parkinson disease (PD).

A total of 120 cases of PD patients who were admitted in our hospital between 2013 and 2015 were enrolled into this study; these 120 cases of PD patients were divided into 3 groups, according to Hoehn–Yahr (H-Y) classification: early stage (1–2 classification), medium stage (2.5–3 classification), and advanced stage (4–5 classification); UA and UA/Cr level in each group was compared. Then, factors including age, gender, dopamine dosage, UA, and UA/Cr levels were analyzed to find the independent predictive factors of PD by logistic regression.

UA and UA/Cr levels in the early and medium stage PD patients were significantly higher than in the advanced stage ones. UA and UA/Cr levels in patients with good prognosis were significantly higher than in the poor ones.

UA and UA/Cr levels are negatively correlated with the stages of PD and are independent negatively predicting biological indexes of PD incidence and progression.

Abbreviations: AD = Alzheimer disease, ALS = amyotrophic lateral sclerosis, HR = hazards ratio, H-Y = Hoehn–Yahr, MSA = multiple system atrophy, PD = Parkinson disease, UA = uric acid, UA/Cr = uric acid/creatinine ratios.

Keywords: H-Y classification, Parkinson disease, prognostic factor, uric acid, uric acid/creatinine

1. Introduction
Parkinson disease (PD) is a common neurodegenerative disease. Its etiology and pathogenesis are very complex, and remains unclear at present. These may be related to the interactions of age, environment, heredity and oxidative stress, and other factors.[1,2] Uric acid (UA) is a natural antioxidant that has effects of scavenging free radicals, and antioxidation.[1,2] It has been reported that serum UA concentrations are closely related to the development of some neurodegenerative diseases such as PD, multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), and Alzheimer disease (AD).[1,6] Therefore, we explored the correlation between this disease classification versus UA and UA/Cr levels by investigating differences in UA and UA/Cr levels in PD patients at the early, medium, and advanced stages.

2. Materials and methods
2.1. Research objects
Hospitalized PD patients admitted in our hospital from 2013 to 2015 were included into this retrospective study. These patients were diagnosed by 2 experienced neurologists, strictly in accordance with the UK Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria. Exclusion criteria were as follows: PD induced by chemical drugs, trauma, cerebrovascular disease, and other reasons; PD patients complicated with nephropathy, tumor, gout, vegetarians; PD patients who received thiazide diuretics and patients of nervous system disease were excluded. All subjects provided a signed informed consent. Among these subjects, 63 subjects were male and 57 subjects were female. The age of these subjects ranged from 27 to 86 years, with an average age of 69.10±0.78 years, and the course of the disease was 0.5 to 20 years. According to the Hoehn–Yahr (H-Y) classification, the 120 PD patients were divided into 3 groups: early stage (1–2 classification, 37 cases), medium stage (2.5–3 classification, 49 cases), and advanced stage (4–5 classification, 34 cases). Then, UA and UA/Cr levels in each group were compared.[1,2] Exclusion criteria included chemical drugs, trauma, cerebrovascular disease, and other causes of PD, and further exclusion of nephropathy, tumor, gout, use of seprazone diuretics, and vegetarians.

This study was conducted in accordance with the declaration of Helsinki.

This study was conducted with approval from the Ethics Committee of Hua’ian First People’s Hospital. Written informed consent was obtained from all participants.

2.2. Methods
Four milliliters of fasted elbow venous blood were collected from all the subjects in the morning, and UA was determined using an
3. Results

Healthy group UA and UA/Cr were higher than pd group. There was no significant difference in age and disease duration between the 3 groups. UA and UA/Cr values in the different classifications of disease conditions in the PD group. When variance analysis was used among groups with different H-Y classifications, statistically significant differences were found in comparison with the 3 groups (F = 42.34, P < .0001), and there were also statistically significant differences in UA/Cr among these 3 groups (F = 63.15, P < .0001). Results of the Turkey HSD test in each group revealed that UA value (3.47 ± 11.36 μmol/L) in the early stage was higher than in the medium (288.60 ± 10.42 μmol/L) and advanced (202.50 ± 8.90 μmol/L) stages in the PD group, and the differences were statistically significant (t = 3.76, P = .0003; and t = 9.90, P < .0001, respectively). UA value in the medium stage (288.60 ± 10.42 μmol/L) was higher than that in the advanced stage (202.50 ± 8.90 μmol/L), and the difference was statistically significant (t = 5.92, P < .0001). UA/Cr value in early stage (5.44 ± 0.13) was higher than in the medium (4.31 ± 0.15) and advanced (3.16 ± 0.10) stages in the PD group, and the difference was statistically significant (t = 5.47, P < .0001; t = 14.3, P < .0001, respectively). UA/Cr value in the medium stage (4.31 ± 0.15) was higher than in the advanced stage (3.16 ± 0.10), and the difference was statistically significant (t = 5.84, P < .0001; Table 1; Fig. 1).

Taking the PD classification as the dependent variable, and taking UA level, UA/Cr ratio, gender, age, and dopamine dose as independent variables, univariate and multivariate ordered logistic regression were carried out. Results revealed that gender, age, and dopamine dose had no correlation with disease conditions, while UA level [hazards ratio (HR): 0.986, 95% confidence interval (95% CI): 0.976–0.995] and UA/Cr value (HR: 0.292, 95% CI: 0.165–0.517) were independent prognostic factors of PD (P < .01). Furthermore, UA/Cr value had a more significant predictability for PD disease (P < .001, Tables 2 and 3).

4. Discussion

PD is a common neurodegenerative disease with main clinical features of resting tremor, bradykinesia, myotonia, and gait posture abnormalities, and is associated with depression, constipation, sleep disorders, and other nonmotor symptoms. Although the pathogenesis of PD remains unclear, oxidative stress has been the hot topic in the research of the pathogenesis of PD. In pathological conditions, there is an overproduction of reactive oxygen and reactive nitrogen may damage cells and almost all DNAs in the mitochondria. More evidences have continued to indicate that oxidative stress could lead to injury of the nigral neurons. UA is a natural antioxidant in blood and the brain. It can reduce brain damage caused by oxidative stress. Studies have shown that more than half of the antioxidant capacities of humans are derived from UA. UA is an important endogenous antioxidant that can scavenge reactive oxygen species (ROS), as well as nitro oxide and chelate ferric.
ions, proving that UA plays an important role in the pathogenesis of PD.\textsuperscript{[4,10–12]} Urate is present in bodily fluids as the anionic form of UA (2,6,8-trioxo-purine). It possesses antioxidant properties comparable to those of ascorbate, and accounts for most of the antioxidant capacity in human plasma.\textsuperscript{[13]} In vitro, in PD models, urate prevents spontaneous degeneration of cultured nigral neurons, as well as dopaminergic cell death induced by oxidative and mitochondrial toxins.\textsuperscript{[14]} In vivo, genetic manipulation of urate oxidase and resulting increased concentrations of urate in the central nervous system (CNS) led to improved phenotype and histopathologic findings in PD mouse models.\textsuperscript{[15]} These data substantiate earlier findings in PC12 cells, in which urate blocked cell death and oxidative damage induced by either dopamine or 6-hydroxydopamine.\textsuperscript{[16]} Radhika and other researchers have found that serum UA levels in PD patients may decrease to levels lower than that in the normal population, through the internal control mechanism. Thus, we can speculate that lower UA may be a potential risk factor for PD.\textsuperscript{[17]} At the same time, foreign scholars have found that higher UA could reduce the risk of PD.\textsuperscript{[18,19]} Furthermore, recent studies have found that in addition to antioxidative stress effects, other mechanisms exist between UA and PD. UA may be involved in the brain neurotransmitter transfer process such as the dopaminergic pathway. Moreover, oxidative stress injury of nigral neurons in patients with PD can lead to lower UA levels. Hence, UA levels can be used not only as an effective monitoring index for the progression of PD but also as a potential neuroprotective agent for the treatment of PD.\textsuperscript{[20–22]} It is noteworthy to mention that UA is primarily metabolized through the kidney, and excreted via urine. Men usually have higher levels of UA than women of the same age, which may be promoted by estrogen. The application of UA/Cr values reduce the interference caused by gender and renal function abnormalities.\textsuperscript{[23]}

In this study, differences in UA and UA/Cr values among the different H-Y classifications of PD patients were compared, and the feasibility of applying UA and UA/Cr values as prognostic indexes for PD disease were further explored. Results revealed that there were differences in UA and UA/Cr values among the different H-Y classifications of PD patients, and these differences were statistically significant. UA in the early stage was higher than in the medium and advanced stages in the PD group; the differences were statistically significant. Furthermore, UA levels in the medium stage were higher than in the advanced stage in the PD group, and the difference was statistically significant. UA/Cr value in the early stage was higher than in the medium and advanced stages in the PD group, and the differences were statistically significant. UA/Cr values in the medium stage were higher than the advanced stage in the PD group, and the difference was statistically significant. Taking UA and UA/Cr values as independent variables for the logistic regression analysis, results revealed that UA and UA/Cr values had correlations with PD. They were independent predictors of PD, and UA/Cr had a more significant correlation with PD.

In conclusion, UA and UA/Cr have an inverse correlation with the H-Y classifications, UA levels gradually decreased with the progression of the disease, and this was consistent with the research conducted by foreign scholars.\textsuperscript{[24–25]} These indicate that lower UA is a risk factor for PD, and UA and UA/Cr can be used as predictive factors for monitoring the progression of the disease, in which UA/Cr values are more effective than UA levels in predicting disease progression.

**Author contributions**

Conceptualization: Ling-Ling Zhong, Ya-Qi Song.

Data curation: Hua Cao, Ke-Ju Ju.

Funding acquisition: Xiang-Yang Tian.

Methodology: Ya-Qi Song, Hua Cao, Ke-Ju Ju.

Validation: Hua Cao, Ke-Ju Ju.

Writing – original draft: Ling-Ling Zhong.

Writing – review & editing: Xiang-Yang Tian.

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