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Clinical Study

Association between serum uric acid and motor subtypes of Parkinson's disease

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ABSTRACT

The aim of this study was to evaluate serum uric acid (UA) levels and serum uric acid/creatinine ratios (UA/Cr) in patients with non-tremor dominant (NTD) Parkinson's disease (PD) compared to tremor dominant (TD) PD and healthy controls (HC). UA is believed to have a protective effect on the central nervous system against oxidative damage and neuronal cell death which could impact on progression and motor subtypes of PD. Serum UA levels and UA/Cr were determined in 100 PD patients and 100 age and sex matched HC. Subtypes of PD were classified into TD and NTD. Patients with PD showed statistically significantly lower serum UA ($p = 0.007$) and serum UA/Cr ratios ($p < 0.001$) than HC. Patients with NTD PD had statistically significantly lower serum UA ($p < 0.001$) and serum UA/Cr ($p = 0.001$) than in patients with TD PD. Patients with mild PD severity also had significantly higher serum UA ($p = 0.015$) and serum UA/Cr ($p = 0.004$) than patients with moderate to severe disease. Our study suggests that UA has a pathogenic role in the clinical subtype of PD. Serum UA levels together with serum UA/Cr are potentially useful biomarkers to indicate risk, severity and motor subtype of PD.

1. Introduction

Parkinson's disease (PD) has high clinical heterogeneity. Within the general diagnosis of PD, various clinical subtypes are identified based on age of onset and the predominant motor sign such as tremor dominant (TD), non-tremor dominant (NTD) and postural instability and gait difficulty. Previous studies have shown that the TD subtype of PD is a favorable prognostic factor and is usually benign in progression. TD patients generally have a better quality of life than NTD [1,2]. *Post mortem* analysis of the brain of TD patients shows significantly less cortical Lewy body deposition than NTD patients [3]. This could possibly reflect evidence of neuroprotective substances in TD patients.

Uric acid (UA) is an antioxidant and iron scavenger in the human body that has been hypothesized to have a protective effect on the central nervous system against oxidative damage and dopaminergic cell death in PD [4,5]. The amount of serum UA is regulated mainly by dietary intake of purines and renal excretion. A reduction in the glomerular filtration rate can increase the level of serum UA and a recent meta-analysis indicated that low serum UA levels are associated with an increased risk and progression of PD [6]. A recent study also showed a negative relationship between UA levels and non-motor symptoms in *de novo* PD patients [7]. Although a relationship between UA levels and PD has been demonstrated, the association of UA and motor subtypes of PD has not been studied. The aim of this cross-sectional study was to evaluate serum UA level as well as serum uric acid/creatinine ratios (UA/Cr) in patients with TD compared to NTD PD and healthy controls (HC).

2. Patients and methods

This study is based on 100 PD patients from the neurology clinic of Thammasat University Hospital between June 2013 to March 2014, and 100 HC from the check-up clinic between 2012 and 2013. The study was approved by the institutional review broad and the ethics committee. PD patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria. HC inclusion criteria were age and sex-matched individuals without a history of any neurological diseases or PD. General demographic data including sex, age, body mass index (BMI), medication history, and levodopa-related motor complications were recorded. Individuals with history of gouty arthritis, abnormal levels of serum creatinine (>1.5 mg/dl) and current use of uric acid lowering agents including allopurinol and diuretics

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were excluded. The first hundred consecutive PD cases that suited the criteria were prospectively enrolled in the study. PD subtypes were classified as TD and NTD according to the method used by Jankovic et al. [8] Motor symptoms were assessed using the unified Parkinson's disease rating scale (UPDRS), modified Hoehn and Yahr (H&Y) stage and the Schwab and England activities of daily living scale (SE-ADL). Non-motor symptoms were assessed using the non-motor symptoms questionnaire (NMSQ), Thai geriatric depression scale-15 (TGDS-15) and the Thai mental state examination (TMSE). Serum UA level and UA/Cr ratio were determined.

Statistical analyses conducted using SPSS statistics (version 13; IBM Corporation, Armonk, NY, USA). Statistical analyses included an unpaired t-test, analysis of variance, correlation coefficients and linear regression analyses, where appropriate. A p value of less than 0.05 was considered statistically significant.

3. Results

A total of 200 people were enrolled in this study, 100 with PD and 100 HC. Thirty-four out of 100 PD patients had the TD subtype and 64% had mild to moderate disease severity (H&Y stage 1–2.5). Clinical and demographic features of the total population are summarized in Table 1. There was no statistically significant difference in sex, age, BMI, blood pressure and serum creatinine level between the groups. Patients with PD had significantly lower mean serum UA ($p = 0.007$) and serum UA/Cr ratio ($p < 0.001$) than the HC (Table 1; Fig. 1). The mean serum UA levels in men were statistically significantly higher than the women in both the PD patients ($p < 0.001$) and HC ($p < 0.001$) but these differences were not observed in serum UA/Cr ratios (Table 1).

Subgroup analysis in patients with PD showed statistically significantly lower UA levels ($p < 0.001$) and serum UA/Cr ratios ($p = 0.001$) in NTD compared to the TD subtype (Table 2; Fig. 2).

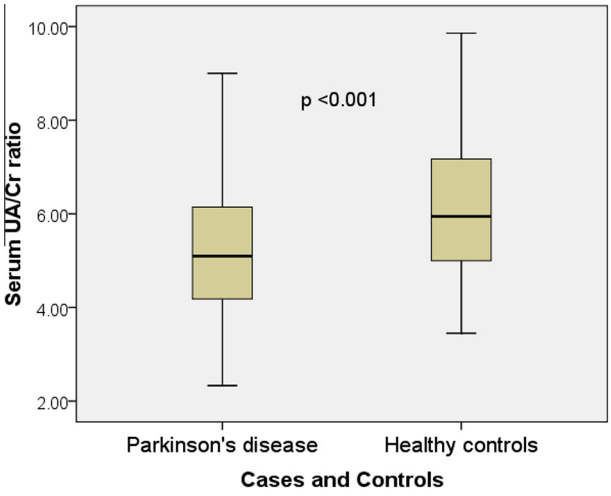

Fig. 1. Serum uric acid/creatinine ratio (UA/Cr) in Parkinson's disease patients and healthy controls.

These observations were seen in both men and women. However, there was no statistically significant difference in UA levels and UA/Cr ratios between patients with the TD subtype and HC. The UPDRS motor score, the UPDRS postural subscore, modified H&Y stage, SE-ADL scale, NMSQ score, total levodopa equivalent dose (LED) and percent of motor complications were statistically significantly higher in the NTD compared to the TD group. There was no significant difference in sex, age, type of anti-kinetic drugs, disease duration and TMSE scores between the groups.

Table 1
Demographic and clinical characteristics of the study participants (n = 200)

	Parkinson's disease (n = 100)	Control (n = 100)	p value
Sex, % men	50	50	-
Age, years			
Total	68.14 ± 11.48	66.31 ± 4.51	0.140
Male	68.44 ± 11.97	67.24 ± 5.08	0.516
Female	67.84 ± 11.09	65.38 ± 3.69	0.142
BMI	23.93 ± 4.57	24.14 ± 4.03	0.765
Hypertension, %	53	48	0.515
Disease duration, years	4.44 ± 4.02	-	-
SE-ADL	75.90 ± 15.90	-	-
H&Y scale	2.33 ± 0.90	-	-
UPDRS motor score	23.41 ± 11.80	-	-
Total LED, mg/day	483.12 ± 369.87	-	-
NMSQuest score	13.15 ± 5.73	-	-
TMSE	25.51 ± 4.46	-	-
Motor complications, %	40	-	-
Serum UA, mg/dl			
Total	5.01 ± 1.46	5.54 ± 1.29	0.007
Male	5.79 ± 1.21	6.20 ± 1.22	0.093
Female	4.24 ± 1.26	4.89 ± 1.01	0.005
Serum Cr, mg/dl			
Total	0.95 ± 0.23	0.92 ± 0.19	0.297
Male	1.13 ± 0.17	1.05 ± 0.15	0.016
Female	0.78 ± 0.14	0.80 ± 0.16	0.649
Serum UA/Cr ratio			
Total	5.36 ± 1.61	6.14 ± 1.54	< 0.001
Male	5.23 ± 1.31	5.98 ± 1.26	0.004
Female	5.48 ± 1.86	6.34 ± 1.73	0.018

All values are shown as the mean ± standard deviation, unless otherwise specified.
- = not applicable, BMI = body mass index, Cr= Creatinine, H&Y = modified Hoen and Yahr stage, LED = levodopa equivalent dose, NMSQ = non-motor symptoms questionnaire, SE-ADL = Schwab and England activities of daily living, TMSE = Thai mental stage examination, UA = uric acid, UPDRS = unified Parkinson's disease rating scale.