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RESEARCH ARTICLE

Correlation of Serum Uric Acid with Cognition, Severity, and Stage of Disease in Patients with Idiopathic Parkinson's Disease and Vascular Parkinsonism: A Cross-Sectional Study

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Abstract:

Background:

Uric acid (UA) being a potent antioxidant may reduce the oxidative stress and progression of Parkinson's disease. However, the role of UA is not yet established in people with Idiopathic Parkinson's disease (IPD) and Vascular Parkinsonism (VP).

Objectives:

We aimed i) to compare the serum UA levels in IPD, VP, and healthy adults and ii) to find a relation between UA levels with disease severity, disease stage, and cognitive function in people with IPD and VP.

Methods:

A cross-sectional study was conducted among people with IPD (n=70), VP (n=70), and healthy adults (n=70). Demographics details, body mass index, duration of illness, levodopa usage, comorbidities, MDS-UPDRS scores, modified H&Y scale, MMSE, and serum UA levels were collected from participants. Pearson's correlation coefficient was used to find the correlation between UA levels, MDS-UPDRS, H & Y, and MMSE scores.

Results:

The age of the participants ranged from 59 to 80 years. Results showed that serum UA level in healthy control (5.41±0.99; p=0.001) and VP groups (5.27 ± 0.99; p=0.001) were significantly higher compared to IPD group (4.34 ±1.03). We found a significant negative correlation between UA and MDS-UPDRS (r=-0.68, p<0.01) and H & Y scores (r = -0.61, p<0.01) and a significant positive correlation of UA with MMSE (r=0.55, p<0.01) in the IPD group. UA levels in the VP group were not correlated with any of the outcome measures.

Conclusion:

In people with IPD, serum UA level was negatively correlated with severity and progression of the disease but positively correlated with cognitive ability.

Keywords: Parkinson's Disease, Antioxidant, Uric acid, Disease progression, Neuromodulation, Cognitive ability.

Article History

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1. INTRODUCTION

Parkinson's disease (PD) affects over 1% of the population above 65 "years "of "age [1]. It "is "a "neurodegenerative "disease

characterized by chronic and progressive loss of dopaminergic neurons in substantia nigra pars compacta [1]. Oxidative stress has been proposed to play a key role in the degeneration of the nigrostriatal dopaminergic pathway and may represent a common central pathway in the complex convergence of genetic and environmental etiologic factors [2]. Oxidative stress takes part in the pathogenesis of PD by enhancing

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enzymatic and non-enzymatic oxidation of dopamine, calcium influx through L-type calcium channels, and PD-linked genes [2]. Oxidative stress intertwines with all other mechanisms that have been implicated in PD, including protein misfolding and aggregation, mitochondrial dysfunction, cell cycle reactivation, apoptosis, and excitotoxicity [3]. Several biological markers of oxidative damage, such as selegiline [4], vitamin E [5], coenzyme 10 (CoQ10) [6], and creatine [7], are elevated that may assist in the early diagnosis and identification of at-risk groups. However, the results have disappointingly failed to show clear benefits.

Uric acid (UA) is an end product of purine metabolism and has been shown to be a potent antioxidant by scavenging hydroxyl radicals and singlet oxygen, thereby decreasing oxidative stress [8]. UA, mainly as the urate in the human body, can scavenge free oxygen radicals and interact with other antioxidant systems and is an important physiological antioxidant [8]. Increasing epidemiological and clinical evidence has shown that higher UA levels were associated with a decreased risk and slower disease progression for PD [9] [10]. Association between levels of UA and PD has gained intensive interest, but results drawn from these studies have been inconsistent [10 - 12].

Limited data on serum UA levels in PD patients or its effect on nonmotor symptoms, such as cognitive decline, is available. Given the lack of treatment to alter the disease course and the high prevalence of cognitive symptoms in PD, we aimed to investigate whether patients with PD have low plasma uric acid levels and whether uric acid contributes to ascertaining the prognosis in PD. In the future, increasing the plasma uric acid level might be a therapeutic option to slow the progression of both motor and cognitive symptoms in PD. Therefore, the objectives of this study were i) to examine whether serum UA level is diminished in patients with Idiopathic Parkinson's disease (IPD) and Vascular Parkinsonism (VP) compared to healthy controls, ii) to compare serum UA levels in patients with IPD and VP, and iii) to find a correlation between serum UA levels and stage of disease using Hoehn and Yahr (H&Y) scale, disease severity using Movement Disorder Society -Unified Parkinson Disease Rating Scale (MDS-UPDRS), and cognitive function using Mini-Mental State Examination (MMSE) scale in IPD and VP.

2. MATERIALS AND METHODS

2.1. Selection Criteria

The study approval was obtained from Institutional Research and Institutional Ethics committee (IEC KMC MLR 04-19/159). This cross-sectional, single-center, open-label study was conducted at the Department of Neurology, Kasturba Medical College Hospital, Mangalore, Manipal Academy of Higher Education, Karnataka, for 12 months from March, 2019, to March, 2020. Patients visiting the Department of Neurology were screened for eligibility criteria, and written informed consents were obtained from agreed participants. We included participants who visited the hospital, fulfilled the diagnostic criteria of PD [13] and VP [14], and gave their written consent. Participants visiting out-department or those who were hospitalized and did not have any neurodegenerative or cerebrovascular diseases were included as controls. We

excluded participants if they had PD with any other somatic disease (pain syndrome, advanced diabetes mellitus, malignancy, renal, hepatic or heart failure, severe anemia, or any other acute or chronic debilitating or life-threatening disease/state), were not willing to give consent, and were receiving treatment with diuretics and antihyperuricemia medication.

2.2. Data Collection

All participants were categorized into three main groups: IPD, VP, and control group. A detailed clinical history and examination were performed for case and control groups. Demographic details and participants' characteristics were collected and consisted of age, gender, body mass index (BMI), duration of illness, levodopa usage, presence of comorbidities, MDS-UPDRS scores, modified H&Y scale, MMSE, and serum UA levels. Non-fasting blood samples were collected from the case and control group participants, and serum UA levels were determined using standard clinical methods.

2.3. Data Analysis

Data were analyzed using SPSS version 25. Descriptive statistics were used to describe demographic variables. Kolmogorov-Smirnov test was performed to test the normality of the data. A comparison of UA levels among the IPD, VP, and control groups was made using ANOVA. Post hoc analysis of UA levels between the groups was performed using an independent sample t-test. Between-group comparisons of BMI, duration of illness, levodopa dosage, MDS-UPDRS, H&Y, and MMSE scores were performed using an independent sample t-test. Pearson's correlation coefficient was used to find a correlation between UA levels and the aforementioned characteristics in IPD and VP groups. The level of significance was taken as $p \leq 0.05$ for ANOVA and independent sample t-test, whereas the level of significance was taken as $p \leq 0.01$ for Pearson's correlation coefficient.

3. RESULTS

Out of 473 participants screened, 210 participants met the inclusion criteria and were recruited for the study. The age of the participants ranged from 59 to 80 years. Mean BMI scores revealed that participants in the IPD and VP groups belonged to a healthy weight category, and participants in the control group belonged to an overweight category. Table 1 illustrates the baseline characteristics of the participants in the three groups.

There was a significant difference in the age of the participants between the IPD and VP groups ($p=0.01$). A significant difference was observed in the MDS-UPDRS scores ($p=0.01$) and MMSE scores ($p<0.0001$) between IPD and VP groups. However, there was no significant difference between groups in BMI, duration of illness, daily levodopa dosage, and H&Y scores.

Analysis of UA levels showed a significant difference between IPD, VP, and control groups ($p<0.0001$). Furthermore, on post hoc analysis, it was found that the serum UA levels in the control group (5.41 ± 0.99 ; $p=0.001$) and VP group (5.27 ± 0.99 ; $p=0.001$) were significantly higher than in the IPD group (4.34 ± 1.03). Table 2 demonstrates the comparison of UA levels between the three groups.

Table 1. Baseline characteristics of the participants (n = 210).

Variables	IPD (n=70)	VP (n=70)	Control (n=70)
Age (Mean ± SD)	69.09±10.61	73.19±7.94	69.08±10.62
Gender, only female (n, %)	23 (32.9%)	20 (28.6%)	38 (54.3%)
BMI (Mean ± SD)	24.58±2.45	24.49±1.79	25.39±1.46
Hypertension (n, %)	42 (60%)	68 (97.14%)	
Diabetes Mellitus (n, %)	29 (41.42%)	45(64.28%)	
Duration of illness	3.21±1.91	3.27±1.69	
Daily levodopa dosage (mg)	302.14±135.25	273.57±106.90	
MDS-UPDRS	58.14±11.96	62.40±8.79	
H & Y	2.37±0.86	2.56±0.95	
MMSE	25.56±2.67	23.97±2.55	

BMI: Body Mass Index; H& Y: Hoehn and Yahr; IPD: Idiopathic Parkinson's Disease; MDS-UPDRS: Movement Disorder Society-Unified Parkinson Disease Rating Scale; MMSE: Mini-Mental State Examination; VP: Vascular Parkinsonism.

Table 2. Comparison of uric acid between the groups.

Comparison of UA levels across IPD, VP and control groups			Post-hoc comparison of UA levels among three groups			
Group	Mean ± SD	F statistic (p-value)	Groups	Mean difference	t value	p-value
IPD	4.34 ± 1.03	24.85 (p<0.0001)**	IPD vs VP	-0.93	-5.68	0.00**
VP	5.27 ± 0.90		IPD vs Control	-1.07	-6.26	0.00**
Control	5.41 ± 0.99		VP vs Control	-0.13	-0.86	0.39

p<0.01 = statistically significant

IPD: Idiopathic Parkinson's Disease; VP: Vascular Parkinsonism.

We assessed the correlation of UA levels with different parameters among IPD and VP groups. UA level showed a significant moderate negative correlation with levodopa dosage, MDRS-UPDRS, UPDRS I, UPDRS II, UPDRS III, UPDRS IV, and H & Y scores in the IPD group. There was a significant moderate positive correlation between the UA levels and MMSE scores in the IPD group. However, UA levels in the VP group were not significantly correlated with any of the parameters. Table 3 shows the correlation of UA with different parameters between the groups.

We conducted a subgroup analysis to identify the correlation of UA levels with different parameters among

males and females within each group (IPD and VP). UA levels among the males in the IPD group showed a mild significant negative correlation for all parameters except BMI and MMSE. MMSE score showed a mild positive correlation with UA in males. There was a significant mild negative correlation with UA and duration of illness, levodopa dosage, UPDRS II, UPDRS IV, and MMSE among females with IPD. While, age, MDRS- UPDRS, UPDRS I, UPDRS III, and H & Y showed a significantly strong negative correlation with the UA levels in females. However, no correlation was observed between BMI and UA levels among both males and females in the IPD group. No correlation was observed between UA and other parameters in the VP group (Table 4).

Table 3. Correlation between UA and various scores in different groups.

	Parameters	IPD		VP	
		r value	p-value	r value	p-value
UA	Levodopa	-0.50	0.001	0.22	0.06
	MDS-UPDRS	-0.68	0.001	0.17	0.14
	UPDRS I	-0.61	0.001	0.21	0.07
	UPDRS II	-0.61	0.001	0.15	0.20
	UPDRS III	-0.69	0.001	0.16	0.18
	UPDRS IV	-0.47	0.001	0.12	0.29
	H & Y	-0.61	0.001	0.09	0.45
	MMSE	0.55	0.001	-0.11	0.32

p<0.01 = statistically significant

H& Y: Hoehn and Yahr; IPD: Idiopathic Parkinson's Disease; MDS-UPDRS: Movement Disorder Society-Unified Parkinson Disease Rating Scale; MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson Disease Rating Scale; VP: Vascular Parkinsonism.

Table 4. Correlation UA and various parameters in the groups of different genders.

	Parameters	IPD				VP			
		Males		Females		Males		Females	
		r value	p value	r value	p value	r value	p value	r value	p value
UA	Age	-0.47	0.001	-0.81	0.001	0.38	0.001	0.14	0.53
	BMI	0.1	0.50	0.19	0.37	0.10	0.46	-0.10	0.65
	Duration	-0.48	0.001	-0.61	0.001	0.19	0.16	0.03	0.87
	Levodopa	-0.4	0.001	-0.56	0.001	0.29	0.03	0.05	0.82
	MDS-UPDRS	-0.6	0.001	-0.77	0.001	0.28	0.04	-0.03	0.89
	UPDRS I	-0.54	0.001	-0.72	0.001	0.32	0.02	-0.01	0.09
	UPDRS II	-0.54	0.001	-0.67	0.001	0.22	0.11	-0.02	0.91
	UPDRS III	-0.61	0.001	-0.78	0.001	0.28	0.04	-0.06	0.79
	UPDRS IV	-0.44	0.001	-0.52	0.001	0.17	0.22	0.03	0.88
	H & Y	-0.51	0.001	-0.76	0.001	0.16	0.26	-0.03	0.87
	MMSE	0.41	0.001	-0.67	0.001	-0.14	0.31	-0.02	0.90

p<0.01 = statistically significant

BMI: Body Mass Index; H& Y: Hoehn and Yahr; IPD: Idiopathic Parkinson's Disease; MDS-UPDRS: Movement Disorder Society-Unified Parkinson Disease Rating Scale; MMSE: Mini-Mental State Examination; UA: Uric Acid; UPDRS: Unified Parkinson Disease Rating Scale; VP: Vascular Parkinsonism.

4. DISCUSSION

This study examined the level of serum UA in patients with PD and normal controls and compared serum UA levels with different disease parameters among patients with IPD and VP. The results showed a correlation between UA levels and severity of disease (MDS-UPDRS), stage of disease (H & Y), and cognitive function (MMSE).

There was a significant difference in the age of participants, disease severity, and cognitive function between the IPD and VP groups. The age difference could be attributed to the difference in etiology as IPD is a neurodegenerative disease characterized by a long-standing progressive loss of dopaminergic neurons in the Substantia Nigra Pars Compacta [15]. VP, on the other hand, is a secondary lesion in the dopaminergic nerves distinguished by microinfarcts within the vessels due to vascular risk factors [16]. The mean age of our participants was similar to that reported in the literature [17].

Our results showed that the serum UA level was significantly higher in the VP and control group compared to the IPD group. Levodopa reduces the transport and excretion of UA through the renal tubular system and therefore increases UA levels and hyperuricemia. It has been reported that chronic administration of levodopa to patients with PD resulted in hyperuricemia and gout [18]. In our study, the mean daily levodopa dosages were similar in both groups, indicating that the significant difference in the UA levels between IPD and VP groups was not due to the difference in levodopa dosage. The duration of illness was similar in both IPD and VP groups, so it could not have influenced the difference in UA levels in both groups.

The disease severity measured using the MDS-UPDRS score was significantly lower in the IPD group compared to the VP group, whereas no difference was observed in the stage of disease measured using H&Y scores between the two groups. Our findings are similar to another study that reported lower UPDRS scores in the IPD group compared to the VP group. It

could be due to the additional cerebrovascular lesions seen in VP, which are absent in IPD [19].

In our study, cognitive functions measured using MMSE scores were significantly higher among IPD compared to the VP group. Our results are similar to a previous study that assessed cognitive impairment among patients with IPD and VP and reported higher cognitive impairment among patients with VP [20]. The reason for this finding is that the neuropathology of cognitive decline in PD includes degeneration of subcortical nuclei with both neuronal loss and Lewy body pathology, which exacerbates the disease progression. Conversely, in VP, cognitive decline can occur early at disease onset due to the involvement of subcortical microvascular structures in the brain and manifests as difficulties in planning, abstract thinking, verbal fluency, judgement, and goal-directed behavior [21]. There is a direct relationship between the severity of cognitive decline and the extent of cell loss in the medial substantia nigra [22].

UA levels were compared across control, IPD, and VP groups, followed by a post hoc analysis. High serum UA levels are associated with greater cerebral vascular lesions [23], which could have led to greater UA levels in the VP group. Similarly, greater UA levels among controls were found in the study conducted by Pan M *et al.*, affirming that a lower level of UA in people with PD is responsible for the oxidative stress within the dopaminergic neurons, leading to further severity [24].

Except for cognitive function, all other parameters had a significant negative correlation with UA in the IPD group, suggesting that lower UA levels in IPD were correlated to higher disease severity and higher disease progression. Our results are supported by findings of other cohorts that have shown the protective role of UA in neurodegenerative diseases, such as Alzheimer's disease [25]. In contrast, cognitive function showed a positive correlation with UA level in the IPD group, suggesting that a higher UA level is correlated with

better cognitive function. In the VP group, none of the parameters were correlated to UA level. Our results are similar to a study conducted by Lei J *et al.*, which estimated the association of serum A β 1-42, cystatin C, and UA in 108 PD patients and 108 healthy individuals and revealed a significant negative correlation between UA, disease severity, and progression measured using UPDRS and H&Y scores [26]. Another study that compared serum UA between cases and controls showed that UA was correlated to the H&Y scores, thus reflecting disease progression and disability [24]. Since UA is correlated with disease severity in PD, it could be used as a predictor of disease severity and progression, whereas UPDRS scores could be used to compare the extent and burden of disease in PD.

A significant positive correlation between serum UA levels and cognitive impairment in the IPD of the present study is similar to another study by Euser *et al.* that assessed the relationship between UA levels and cognitive function. They reported a better cognitive ability in people with higher UA levels at baseline in all cognitive domains [27].

Our study had a few limitations. We included participants in the control group who visited the outpatient department for routine medical check-ups, dental issues, and other minor ailments and did not have any neurodegenerative or cerebrovascular diseases. Even though these health issues are less likely to influence serum uric acid levels, healthy adults would have provided a more accurate comparison of uric acid levels with the healthy population. We did not include the role of lifestyle factors, such as diet, smoking, alcohol, and exercise and genetic factors, such as SLC22A12 and xanthine oxidoreductase polymorphisms, that could have influenced the results. Moreover, our participants had a short duration of disease (around 3.5 years), so our findings could not be applied to longstanding cases of PD. However, this is one of the first few studies that have ascertained the relationship between serum UA levels with cognitive function, disease progression, and severity in PD.

CONCLUSION

Lower serum UA level was seen in people with IPD compared to VP and normal adults. In people with IPD, the severity of the disease increases with a reduction in serum UA levels. This correlation was not seen in people with VP. Future studies should aim at establishing the temporal association between UA levels and disease severity as well as considering the role of dietary and lifestyle factors on disease progression. UA levels can be used as a diagnostic tool to detect a cognitive decline in PD, thereby assisting in the early detection and management of the disease.

LIST OF ABBREVIATIONS

IPD	=	Idiopathic Parkinson's disease
VP	=	Vascular Parkinsonism
PD	=	Parkinson's disease

AUTHORS' CONTRIBUTIONS

ZK, SA, and UB participated in the conceptualization of

the idea and protocol development. SP collected the data. SP, AM, and PN analyzed the data and prepared the manuscript draft. All authors contributed to the drafting and revision of the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study approval was obtained from the Institutional Research and Institutional Ethics committee of Kasturba Medical College, Mangalore (IEC KMC MLR 04-19/159).

HUMAN AND ANIMAL RIGHTS

No animals were used in the studies that are the basis of this research. This research was conducted on humans in accordance with Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

CONSENT FOR PUBLICATION

Patients visiting the Department of Neurology were screened for eligibility criteria, and written informed consents were obtained from agreed participants.

STANDARDS FOR REPORTING

STROBE guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author [A.M].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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