Serum Uric Acid and Manganese as Potential Biomarkers in Parkinson's Disease and Vascular Parkinsonism

Original Article

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ABSTRACT

Objective: This research seeks to explore the relationship between serum concentrations of uric acid (UA) and manganese (Mn) in individuals diagnosed with Parkinson's disease (PD) and vascular parkinsonism (VP).

Methods: A cross-sectional study was conducted on 20 patients diagnosed with idiopathic PD, following the UK PD Society Brain Bank criteria, and 20 patients diagnosed with VP, based on Zijlmans' criteria. Participants were enrolled from the movement disorders outpatient clinics at Ain Shams University and Helwan University Hospitals between April and December 2018. Motor impairment and disease severity were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS-III). Non-fasting blood samples were obtained and centrifuged to determine serum UA and Mn levels.

Results: A significant difference in serum UA and Mn levels was observed between PD and VP patients. VP patients exhibited higher mean UA levels, whereas PD patients had elevated Mn levels. No significant correlation was found between serum UA levels and UPDRS-III scores, daily L-dopa dosage, or disease duration in either group. However, in VP patients, a significant inverse correlation was noted between age, daily L-dopa dosage, UA, and Mn levels. In contrast, no significant correlation was found in PD patients between demographic data (age, sex), clinical data (UPDRS-III scores, disease duration, daily L-dopa dosage), UA levels, MRI findings, and Mn levels.

Conclusion: Serum UA and Mn levels may serve as potential biomarkers to distinguish VP from PD. Mn levels ≥2.15 can differentiate PD from VP with 90% sensitivity and 75% specificity, while UA levels ≤5.35 can distinguish PD from VP with 75% sensitivity and 95% specificity.

Key Words: Biomarkers, idiopathic parkinson disease, manganese, uric acid, vascular parkinsonism.

Received: 25 January 2025, **Accepted:** 23 February 2025.

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ISSN: 2735-3540, Vol. 76, No. 1, March 2025.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease. It is primarily associated with oscillatory dysfunction in basal ganglia circuits, leading to motor and non-motor symptoms and signs. (***Pan et al., 2013***)[1].

Studies have demonstrated the presence of inflammatory responses in the Nigro striatum affected by dopaminergic degeneration, with some certain mechanisms helping to mitigate oxidative stress and inflammation. In recent years, particular focus has been placed on inflammatory mediators that exert antioxidant effects on neurons. (***Pan et al., 2013***)[1].

Vascular Parkinsonism (VP) is caused by cerebrovascular disease, presenting with distinct clinical and pathological features that differentiate it from sporadic Parkinson's disease. It's prevalence is 3–6% among parkinsonian syndromes and is characterized by symptoms such as pronounced bradykinesia, primarily affecting lower body in addition to other traditional Parkinsonism signs and symptoms. Those patients usually experience cognitive impairment, and pyramidal signs. (***Vizcarra et al., 2015***)[2].

Levodopa treatment has shown a response in up to 50% of patients with vascular parkinsonism, especially in cases where lesions are located in or near the nigrostriatal pathways. However, long-term effectiveness is observed in only a limited number of patients. (***Vale et al., 2012***)[3].

DOI: 10.21608/ASMJ.2025.355356.1375

The primary risk factors for vascular parkinsonism closely align with those of cerebrovascular disease, making their prevention and management crucial. A greater cerebrovascular burden is linked to reduced success in rehabilitation outcomes. (***Antonini et al., 2012***)[4].

Uric acid is the final metabolite produced during the breakdown of purines and serves as a key antioxidant in bodily fluids. Fluctuations in serum uric acid levels have been connected to a range of health conditions. Increased uric acid levels are associated with disorders such as gout, hypertension, cardiovascular disease, stroke, and kidney disease, whereas decreased levels have been linked to neurodegenerative and inflammatory conditions, including Parkinson's disease, Alzheimer's disease, multiple sclerosis, and optic neuritis (***Pan et al., 2013***).[1].

Multiple studies have indicated that elevated uric acid levels (hyperuricemia) may help protect against the Gradual deterioration of dopamine-producing neurons in Parkinson's disease by mitigating oxidative stress. (***Poewe et al., 2017***)[5].

Uric acid (UA) has been studied for its effects on vascular physiology, with elevated levels associated with arterial stiffness, endothelial dysfunction, and impaired vasodilation. It may contribute to vascular damage by promoting LDL-C oxidation, granulocyte adhesion, and macrophage infiltration. While typically an antioxidant, UA can act as a pro-oxidant under certain conditions, leading to oxidative stress. This oxidative damage is linked to cerebral ischemia and increased infarct size, which may contreibute in the development of vascular parkinsonism. (***Pan et al., 2013***)[1].

Seifar et al. (2022)[6] examined the significance of uric acid as an antioxidant and proposed that its exclusion from the brain may serve as a protective mechanism against neurodegeneration. They also explored the possibility that Parkinson's disease (PD) itself contributes to low serum UA levels. Additionally, the study suggested that UA could serve as a potential biomarker for disease processes in PD[6].

Manganese is essential for enzyme regulation and physiological functions, primarily through Mn-Superoxide Dismutase (Mn-SOD). Highly expressed in the cerebral endothelium, Mn-SOD helps manage oxidative stress at the blood-brain barrier. Its role in vascular health includes protecting against mitochondrial DNA damage and reducing atherosclerosis risk. ***(Lien et al., 2017***)[7].

Chronic Mn exposure was found to be associated with Parkinson's disease, though its exact role remains unclear. Studies show that Mn accumulation reduces dopamine levels and induces PD-like mechanisms, including oxidative stress, glutamate transporter dysfunction, and α-synuclein aggregation. (***Du et al.,2018***)[8].

AIM OF THE WORK

Our aim is to study serum biomarkers (Uric acid and Manganese) as a potential markers for the differentiation of vascular Parkinsonism from idiopathic Parkinson's disease.

PATIENTS AND METHODS

A cross-sectional study was conducted on 40 patients diagnosed with parkinsonism, with an average age of 64.40±9.37 years. These patients were divided into two groups: Group 1 consisted of 20 patients diagnosed with Parkinson's disease based on the UK PD Society Brain Bank criteria (***Hughes et al., 1992***)[9], while Group 2 included 20 patients diagnosed with vascular parkinsonism (VP) according to Zijlmans' criteria (***Zijlmans et al., 2004***)[10]. Participants were enrolled from the outpatient movement disorders clinics at Ain Shams University and Helwan University Hospitals between April and December 2018. The UPDRS-III motor scale was used to assess motor dysfunction and disease severity.

Serum UA and Mn Measurement

Blood samples without fasting were collected from all participants and processed for analysis. Venous blood samples for uric acid measurement were drawn and centrifuged at 3,000 rpm for 10 minutes, with serum separated within one hour. The samples were then stored at –20°C until laboratory analysis. UA levels were measured using a Biochemical Analyzer 7180-ISE with the URO-PAP assay method.

For manganese analysis, blood samples were collected in empty tubes and immediately refrigerated at 4°C. The serum was separated through centrifugation at 3,000 rpm for 10 minutes and stored in plastic tubes at –80°C. Mn levels were determined using an Atomic Absorption Spectrophotometer (UNICAM-929).

Statements and Declaration:

This manuscript was developed following the guidelines outlined in the STROBE Statement Checklist[11]. The study adhered to the ethical principles set forth in the Declaration of Helsinki, and informed consent was secured from all participants prior to their involvement. To ensure patient privacy, all data were anonymized before analysis, and confidentiality was upheld throughout the research process

Conflict of Interest Status:

The authors confirm that there are no direct or indirect conflicts of interest. This study was not supported by any external funding and was entirely self-financed.

Statistical Analysis:

The gathered data underwent a thorough review, coding, structuring, and evaluation using the Statistical Package for Social Sciences (SPSS), Version 20.0 (IBM Corp., Released 2011, Armonk, NY, USA). The selection of statistical methods and data presentation depended on the nature of the variables analyzed.

I. Descriptive Statistics

1. The normality of numerical data distribution was examined utilizing the Kolmogorov-Smirnov test. Parametric numerical variables were summarized as mean (± standard deviation), whereas non-parametric numerical data were represented as the median and interquartile range.

2. Categorical (non-numerical) variables were described using frequencies and corresponding percentages.

II. Inferential Statistics

1. The student's t-test was applied to compare the mean values between two groups for parametric data.

2. The Chi-square test was utilized to evaluate associations between categorical variables.

3. The Mann-Whitney U test was employed to assess differences between two groups in non-parametric numerical data.

4. Correlation analysis, using Pearson's or Spearman's method, was conducted to determine the strength and direction of relationships between two quantitative variables, with correlation coefficients (r/rho) indicating the magnitude and trend.

5. Receiver Operating Characteristic (ROC) Curve analysis was performed to assess the sensitivity and specificity of quantitative diagnostic parameters in distinguishing between two groups.

Significance Threshold (*P-value* Interpretation)

- $P > 0.05$: Not statistically significant (NS)
- $P < 0.05$: Statistically significant (S)
- $P < 0.01$: Highly significant (HS)

RESULTS

The 20 PD patients and 20 VP patients were matched based on age and sex. Mean age of PD patients was (58.50 ±11.38), range (36 - 80 years) and 13(65%) were males, 7(35%) were females. The average disease duration (years) was 4.70 ±3.16. The mean daily L-dopa dosage (mg) 382.50 ±163.25. The mean UPDRS (III) score was 40.30 ±12.01. The mean Uric acid level was 4.85 ±0.84. The mean manganese level was 4.74 ±2.69.

Mean age of VP Patients was (64.40 ± 9.372), range (46 - 97 years) and 15 (75 %) were males, 5(25%) were females. The mean duration of disease (years) 3.10 ±1.48. The mean daily L-dopa dosage (mg) 340.00 ±123.12. The mean UPDRS (III) score was 39.65 ±9.71. The mean Uric acid was 6.15 ±0.6. The mean manganese level was 1.83 ±1.04.

No Notable difference was observed between PD and VD as regard age, sex, disease duration, L-Dopa dosage or UPDRS (III) (Table 1).

A statistically significant difference was evident between PD and VD cases as regard uric acid and manganese. Higher mean uric acid among VD cases (6.15±0.6 vs 4.85± 0.84). Higher manganese among PD cases (4.74±2.69 and a median of 4.1 vs 1.83±1.04 and a median of 1.7).

Table 1: Comparison between PD and VP as regard lab data.

	Diagnosis									*P*	Sig
	PD					VP					
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR		
Uric acid	4.85	±0.84	4.75	4.20	5.45	6.15	±0.60	6.30	5.75 6.65	0.0001*	HS
Manganese	4.74	±2.69	4.10	3.20	5.45	1.83	±1.04	1.70	1.01 2.45	0.0001**	HS

*Student t test **Mann-Whitney Test

Using ROC curve, it was shown that uric acid could discriminate PD from VD cases at a level of ≤5.35 with 75% and 95% sensitivity and specificity respectively (Table 2).

Table 2: ROC curve using uric acid to discriminate PD from VP case.

Cutoff level	AUC (CI)*	Sensitivity	Specificity	PPV**	NPV***	*P*	Sig
Uric acid ≤5.35	0.89(0.762 to 0.971)	75.00	95.00	93.7	79.2	0.001	HS

*Area under Curve (Confidence Interval)
**Positive predictive value
***Negative predictive value

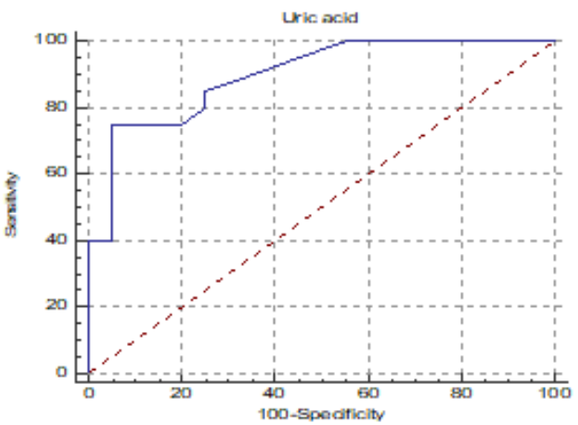

Table 3: ROC curve using Manganese to discriminate PD from VP case.

Cutoff level	AUC (CI)*	Sensitivity	Specificity	PPV**	NPV***	*P*	Sig
Mn≥2.15	0.879(0.737 to 0.960)	90.00	75.00	78.3	88.2	0.001	HS

*Area under Curve (Confidence Interval)
**Positive predictive value
***Negative predictive value

Using ROC curve, it was shown that Manganese could discriminate PD from VP cases at a level of ≥2.15 with 90% and 75% sensitivity and specificity respectively (Table 3).

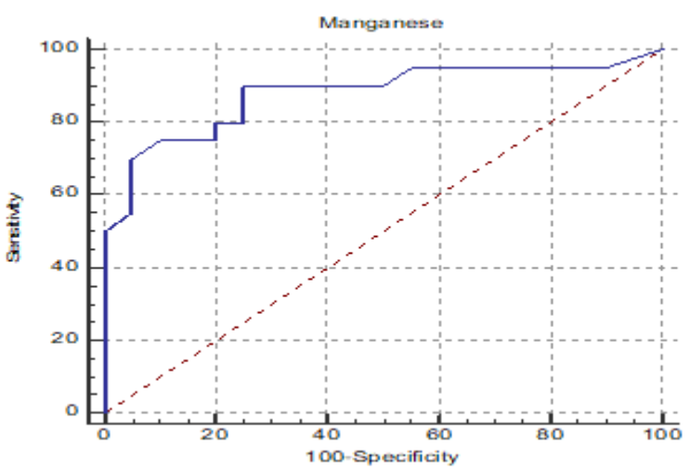

Table 4: Correlation between personal data, medical data and uric acid, manganese among PD cases

		Uric acid		Manganese
Age	r*	0.440	r*	0.313
	p	0.052	*p*	0.179
	Sig	NS	Sig	NS
Duration, years	rho**	0.102	rho**	-0.081
	p	0.667	*p*	0.736
	Sig	NS	Sig	NS
Daily L -dopa dosage, mg	rho**	-0.367	rho**	-0.367
	p	0.111	*p*	0.112
	Sig	NS	Sig	NS
UPDRS(III)	r*	-0.016	r*	0.044
	p	0.946	*p*	0.854
	Sig	NS	Sig	NS
			rho**	0.209
uric acid			*p*	0.377
			Sig	NS

*Pearson correlation **Spearman correlation

There was no significant correlation between personal data, medical data and uric acid, manganese among PD cases (Table 4).

Table 5: Comparison between males and females as regard lab data among PD cases and among VP cases.

	Gender										*P*	Sig
	Male					female						
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
Manganese in PD	5.00	±3.01	4.30	3.60	5.20	4.27	±2.10	3.90	2.90	5.70	0.074**	NS
Uric acid in PD	5.09	±0.87	5.20	4.50	5.80	4.40	±0.63	4.30	3.90	5.10	0.579*	NS
Uric acid in VP	6.00	.60	6.20	5.50	6.50	6.60	.29	6.70	6.40	6.80	0.048	S
Manganese in VP	1.87	1.07	1.80	1.00	2.80	1.71	1.04	1.50	1.04	1.60	0.726	NS

*Student t test **Mann-Whitney Test

There was no significant correlation between males and females according to uric acid and manganese level among PD cases. There was no significant correlation between males and females according to manganese level, however there was significant relationship between males and females according to uric acid level among VP cases (Table 5).

Table 6: Correlation between personal data, medical data and uric acid, manganese among VP cases.

		Uric acid		Manganese
Age	r*	-0.477	r*	.572
	p	0.034	*p*	.008
	Sig	S	Sig	HS
Duration, years	rho**	-0.178	rho**	-.013
	p	0.452	*p*	.956
	Sig	NS	Sig	NS
Daily L -dopa dosage, mg	rho**	0.215	rho**	-.452
	p	0.363	*p*	.046
	Sig	NS	Sig	S
UPDRS(III)	r*	-0.004	r*	.087
	p	0.986	*p*	.716
	Sig	NS	Sig	NS
			rho**	-.511
Uric acid			*p*	.021
			Sig	S

*Pearson correlation **Spearman correlation

There was no significant correlation between medical data and uric acid among VP cases. However, a significant inverse correlation was found between age and uric acid. There was significant positive correlation between age and manganese level, significant negative correlation was found between daily L-dopa dosage (mg), uric acid and manganese level in VP cases (Table 6).

Table 7: Comparison between mild and moderate MRI VP cases as regard lab data.

	MRI Finding										*P*	Sig
	Mild					Moderate						
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
Uric acid	6.33	.39	6.35	6.20	6.65	5.88	.76	5.75	5.45	6.55	0.150*	NS
Manganese	1.80	1.00	1.55	1.03	2.60	1.89	1.15	1.95	.90	2.45	1.0**	NS

*Student t test **Mann-Whitney Test

There was no significant correlation between MRI finding and level of manganese and uric acid in VP cases (Table 7).

DISCUSSION

There were very limited published data on using Uric acid as biomarker in differentiating between PD and VP patients. In our study we found highly significant statistical differences ($p \leq 0.001$) regarding Uric acid between PD cases and VP Cases (6.15±0.6 vs 4.85± 0.84, respectively).

The ROC curve analysis demonstrated that uric acid was effective in distinguishing Parkinson's disease from vascular parkinsonism at a threshold of ≤5.35, with a sensitivity of 75% and specificity of 95%. This finding aligns with previous research indicating that the mean UA level in VP patients exhibited significantly higher levels than those with PD ($p = 0.017$), whereas UA levels in PD patients were considerably lower than in healthy controls ($p = 0.001$) (***Pan et al., 2013***)[1].

These results align with previous findings from multiple longitudinal studies, which suggest Elevated plasma urate levels have been linked to a reduced risk of developing Parkinson's disease (***De Lau et al., 2005; Gao et al., 2016***)[12,13]. Additionally, a review of twelve studies by Yu and colleagues in 2017[14] reported consistently lower uric acid levels in PD patients. A meta-analysis of thirteen studies that was done by (Wen and co-workers in 2017)[15]

further confirmed that Serum uric acid levels are markedly reduced in Parkinson's disease and continue to decline as the disease progresses, suggesting its potential role as an indicator for Parkinson's disease risk and progression. Similarly, Seifar and colleagues in 2022[6] proposed that UA could serve as a biomarker for disease processes in PD.

Regarding gender differences, a significant association was found between males and females in terms of uric acid levels. However, among Parkinson's disease patients, no significant correlation was observed between UA levels and gender in our study. Notably, female patients with vascular parkinsonism had significantly higher UA levels than female PD patients ($p = 0.002$), and female PD patients had lower UA levels than healthy female subjects ($p = 0.007$). Conversely, serum UA levels showed no significant variation between males and females among normal subjects or VP patients. Interestingly, no significant differences in UA levels were detected among normal male subjects, PD, or VP patients (***Pan et al., 2013***)[1]. Similarly, another study by (De Lau and co-workers in 2005)[12] found no significant gender-based differences in UA levels.

Although UA levels did not significantly differ between normal subjects and VP patients, the findings strongly suggest that low serum UA levels may function as a risk indicator or an indirect biomarker for predicting Parkinson's disease, but not vascular parkinsonism (***Pan et al., 2013***)[1].

Our statistical analysis revealed no significant correlation between serum uric acid levels and UPDRS-III scores, daily L-dopa dosage, or disease duration in both Parkinson's disease (PD) and vascular parkinsonism patients ($p > 0.05$). The respective *p-values* were 0.667, 0.111, and 0.946 in the PD group and 0.986, 0.363, and 0.452 in the VP group. These findings contrast with those of ***Pan et al.***,[1] who reported a significant association between serum UA levels and age, BMI, UPDRS-III, H&Y, MMSE, daily L-dopa dosage, and NMSS in PD patients but not in VP patients.

Similarly, A prior study found that serum uric acid levels were lower and exhibited a negative correlation with the duration of Parkinson's disease, UPDRS-III scores, and H&Y staging in both male and female patients (***Ikeda et al., 2011***)[16].

Recent studies suggest that uric acid's neuroprotective effect may be linked to its role as an antioxidant and its ability to modulate neuroinflammation. Elevated uric acid levels have been found to reduce oxidative stress by scavenging reactive oxygen species, thereby mitigating neuronal degeneration (***Bowman et al., 2018***)[17]. However, conflicting evidence suggests that hyperuricemia may contribute to endothelial dysfunction and increase the risk of cerebrovascular diseases, which are primary risk factors for VP (***Latif et al., 2020***)[18]. This paradox highlights the need for further research to determine the exact role of uric acid in neurodegeneration and its potential clinical utility as a biomarker.

Our study revealed a highly significant difference in manganese levels between Parkinson's disease and vascular parkinsonism patients, with higher Mn levels in PD cases ($p = 0.0001$). ROC curve analysis demonstrated that Mn could effectively distinguish PD from VP at a threshold of ≥2.15, with a sensitivity of 90% and specificity of 75%.

Previous studies have not specifically compared serum Mn levels between PD and VP patients. However, a joint analysis of studies examining Mn levels in peripheral blood, including serum, plasma, and whole blood, indicated that PD patients exhibited higher Mn levels compared to healthy controls; however, the difference was not statistically significant after adjusting for age, sex, UPDRS-III scores, daily L-dopa dosage, and disease duration (***Forte et al., 2004; Fukushima et al., 2010; Du et al., 2018***)[19,20,8].

Conversely, another study by Verma and co-workers in 2016[21] reported a significant increase in Mn levels among patients with a disease duration exceeding two years compared to those with a disease duration of two years or less.

In our study, a significant negative correlation was observed between age, daily L-dopa dosage, uric acid, and manganese levels in vascular parkinsonism patients ($p = 0.008$, 0.021, and 0.046, respectively). However, no significant correlation was found between UPDRS-III scores or disease duration in VP cases ($p = 0.087$ and 0.956, respectively).

Among Parkinson's disease patients, no significant correlation was identified between personal factors (age and sex), clinical data (UPDRS-III, disease duration, daily L-dopa dosage), uric acid levels, or MRI findings in relation to manganese levels. The corresponding *p-values* were 0.179, 0.074, 0.854, 0.736, 0.112, 0.377, and 1.0, respectively.

CONCLUSION

Our findings indicate that serum uric acid and manganese levels may serve as valuable biomarkers in differentiating Parkinson's disease from vascular parkinsonism. Elevated manganese levels in PD patients and higher uric acid levels in VP patients suggest distinct pathophysiological mechanisms underlying these conditions. The high sensitivity and specificity of Mn (≥2.15) and UA (≤5.35) thresholds provide potential diagnostic utility.

RECOMMENDATIONS

Further extensive, long-term studies are required to validate the effectiveness of uric acid and manganese as distinguishing biomarkers for Parkinson's disease (PD) and vascular parkinsonism (VP). Exploring the interplay between oxidative stress and neuroinflammation in connection with these biomarkers could offer a more profound understanding of the underlying disease mechanisms. Moreover, combining biomarker evaluation with neuroimaging and genetic research may enhance diagnostic precision and facilitate better patient classification, paving the way for more tailored therapeutic strategies.

STATEMENT AND DECLARATION

This Manuscript was written according to the STROBE Statement Checklist[11]. And The study adhered to the Declaration of Helsinki, and informed consent was obtained from all participants before inclusion. Patient confidentiality was ensured throughout the research process, with data anonymized prior to analysis.

This Manuscript derived from a master thesis approved by Faculty of Medicine, Ain Shams University in 2018. Ethical approval no. is not applicable for this study at that time.

CONFLICT OF INTERESTS

There is no conflicts of interest.

The authors declare that there are no direct or indirect conflicts of interest. This study did not receive any external funding and was entirely self-funded.

AUTHORS' ROLE

A.M. and M.H put the main idea, A.M and A.A collected the data, A.A was responsible for data curation, A.M was responsible for the formal analysis, A.M, K.A and M.H revised the methodology, A.M, A.A and H.K wrote the main manuscript, M.H, K.A and A.M revised the manuscript. H.K and A.M edited the Manuscript.

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حمض اليوريك في الدم والمنغنيز كعلامات بيولوجية محتملة في مرض باركنسون والشلل الرعاش الوعائي

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قسم طب المخ و الأعصاب، كلية الطب، جامعة عين شمس

الهدف: دراسة العلاقة بين مستوى حمض اليوريك أسيد و المنغنيز في الدم لدى مرضى الشلل الرعاش و مرضى الشلل الوعائي.

الطرق: تم إجراء هذه الدراسة المقطعية على ٢٠ مريضًا مصابين بالشلل الرعاشي (PD) وفقًا لمعايير بنك الدماغ لجمعية الشلل الرعاشي في المملكة المتحدة لتشخيص الشلل الرعاشي مجهول السبب، و٢٠ مريضًا مصابين بالشلل الوعائي (VP) وفقًا لمعايير زيلمانز لتشخيص الشلل الوعائي. تم اختيار المشاركين من عيادات اضطرابات الحركة الخارجية بمستشفيات جامعة عين شمس وجامعة حلوان في الفترة من أبريل إلى ديسمبر ٢٠١٨.

تم تقييم اضطرابات الحركة وشدة المرض باستخدام الجزء الثالث من مقياس تقييم مرض الشلل الرعاشي الموحد، تم جمع عينات دم غير صائمة وتم فصلها لقياس مستويات حمض اليوريك والمنغنيز.

النتائج: أظهرت النتائج وجود فرق كبير بين مرضى الشلل الرعاشي و مرضى الشلل الوعائي من حيث مستويات حمض اليوريك والمنغنيز. كانت مستويات حمض اليوريك أعلى في مرضى الشلل الوعائي، بينما كانت مستويات المنغنيز أعلى في مرضى الشلل الرعاشي.

لم يتم العثور على علاقة ذات دلالة احصائية بين تركيز حمض اليوريك في الدم و درجات شدة المرض باستخدام الجزء الثالث من مقياس الشلل الرعاش الموحد، أو الجرعة اليومية من الليفودوبا في المجموعتين. و مع ذلك أظهرت الدراسة علاقة سلبية ذات دلالة احصائية بين العمر و الجرعة اليومية من ليفودوبا و مستويات حمض اليوريك و المنغنيز.

لم تكن هناك علاقة ذات دلالة احصائية بين البيانات الشخصية (العمر و الجنس) أو البيانات الطبية، نتائج التصوير بالرنين المغناطيسي، شدة المرض، ومدة المرض، الجرعة اليومية من الليفودوبا، و مستويات حمض اليوريك أسيد و المنجنيز.

الاستنتاج: يمكن استخدام مستويات حمض اليوريك والمنغنيز كعلامات حيوية غير مباشرة للتمييز بين مرضى الشلل الوعائي ومرضى الشلل الرعاشي. يمكن أن تميز مستويات المنغنيز ≤٢,١٥ مرضى الشلل الرعاشي عن مرضى الشلل الوعائي بحساسية ٩٠٪ وخصوصية ٧٥٪. بينما يمكن لمستويات حمض اليوريك ≤٥,٣٥ التمييز بين المرضين بحساسية ٧٥٪ وخصوصية ٩٥٪.