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URIC ACID A NEUROPROTECTIVE BIOMARKER OF PARKINSON 'S DISEASE

Neurology

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ABSTRACT

AIM: Uric acid an antioxidant prevent oxidative and neuronal death in Parkinson's disease [PD] patients. In humans half of the antioxidant property of blood comes from uric acid. We analyzed Serum Uric Acid in controls and PD patients and its relation to stage and duration of disease.

MATERIALS AND METHODS: Eighty nine PD patients with normal BMI attending our movement disorder clinic were analyzed with serum uric acid levels. Those having diabetes mellitus, hypertension, smoker, alcoholic, renal failure, obesity, anemia and drugs modifying uric acid were excluded from the study. Modified Hoehn And Yahr Staging was done. Eighty nine age and sex matched normal people were taken as controls

RESULTS: Among 89 patients, 68 were males and 21 females. Uric acid levels found significantly reduced in PD compared to controls [5.13 VS 6.4]. Based on Modified Hoehn And Yahr staging 23{25.84%} patients belonged to stage I of,:32{35.95%} in stage II; 22 {24.72% } in stage III AND 12[13.48% } in stage IV. Serum Uric acid levels is found inversely related to staging and duration of illness

CONCLUSION: Serum uric acid is significantly reduced in PD. It correlates with Modified Hoehn And Yahr Staging and duration of illness. Reduction in uric acid level is associated with increased risk of Parkinson's disease[PD] and hyperuricemia acts as a neuroprotective marker from PD .Diet modifications ,iron, zinc supplements increase uric acid; their role in preventing and reducing the morbidity of PD to be confirmed with larger studies

KEYWORDS

uric acid, Parkinson disease, Antioxidant , Hyperuricemia

INTRODUCTION

Parkinson's disease (PD) a chronic neurodegenerative progressive neurological disease having clinical features of rigidity, bradykinesia, rest tremor and postural instability [1] . Asymmetry is a prominent clinical feature of PD which ranks second among the common neurodegenerative disease after Alzheimer's dementia.

The pathological characteristic of PD is intraneuronal alpha synuclein positive Lewy bodies and neuronal cellular loss. Apart from classical motor symptoms PD patients also develop non-motor symptoms. Uric acid, an antioxidant is seen in high concentrations in serum and in the brain, protect against oxidative damage and cell death in PD [2]. Uric acid a powerful antioxidant prevent oxidative and neuronal death in PD patients. In humans half of the antioxidant property of blood comes from uric acid. The study analyzed if there is a significant correlation of mean serum uric acid levels in PD patients when compared to controls. Also we analyzed Serum Uric Acid in PD patients with normal controls and its relation to stage and duration of disease.

AIMS AND OBJECTIVES

Our aim of study is to assess whether there is a significant correlation of reduction of average uric acid levels in PD patients when compared to controls. Also to study Is there a significant correlation of reduction of average uric acid levels in both sexes of PD patients as stages worsen and is there a significant correlation of reduction of average uric acid levels in PD patients as duration of Parkinson disease advances.

METHODS AND MATERIALS

STUDY DESIGN

This study was conducted in Institute of Neurology, Madras Medical College Chennai, Tamil Nadu, India during 2011 to 2013. Informed and written consent were obtained in patient's own language before their inclusion in the study. Eighty nine Parkinson disease patients with normal BMI attending our movement disorder fulfilling the criteria of Parkinson's disease brain bank society [3,4] were included in the study. They include outpatients and inpatients of our hospital. Eighty nine age and sex matched normal people were taken as controls

INCLUSION CRITERIA

All the patients fulfilling the criteria of Parkinson's Disease Society Brain Bank [3,4] were included in the study. All the patients were clinically examined with proper history, clinical features and symptoms. The patients were graded using the Hoehn and Yahr staging system.

EXCLUSION CRITERIA

All the patients with other central or peripheral nervous system disease, Parkinson plus syndromes were excluded from the study. Those having diabetes mellitus, hypertension, smoker, alcoholic, renal failure, obesity, anemia , Patients receiving drugs altering Serum uric acid levels like Diuretics, Angiotensin receptor blockers, Allopurinol, Febuxostat, Atorvastatin, Fenofibrate; Active infections; Cancer Patients and patients on Chemotherapy; Hepatic or renal diseases; Thyroid disorders; Chronic obstructive lung disease; Inflammatory bowel disease and Gout were excluded from the study.

Hoehn And Yahr Staging [5]

- Stage I: Only unilateral involvement, usually with minimal or no functional disability
- Stage II: Bilateral disease or midline involvement without impairment of balance
- Stage III: Mild to moderate bilateral disease with impaired postural reflexes; physically independent
- Stage IV: Severe disabling disease; still able to walk or stand unassisted
- Stage V: Wheel chair bound or confinement to bed unless aided.

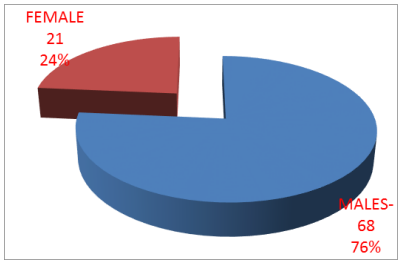
Controls should belong to the same population as the cases.[6,7] The controls are age and sex matched patients attending in our medical outpatient department without diabetes mellitus, hypertension, smoking, alcoholic, renal failure, obesity, anemia , hypouricemic drugs All patients and control group were informed and the consent was obtained. Age, Sex, History of Smoking, Alcoholism, Diabetes Mellitus, Hypertension and their duration was asked from the study groups. Baseline blood pressure was recorded in supine posture on admission. Within 24 hours of admission into the hospital, blood samples were collected from the study groups and their Serum Uric Acid (Uricase Method), Fasting Blood Sugar (GOD-POD method), Total Cholesterol (Direct Method), Triglyceride (Direct Method), Very Low Density Lipoprotein (Direct Method), Low Density Lipoprotein (Direct Method), High Density Lipoprotein (Direct Method) Urea and Creatinine (Kinetic methods) levels were estimated in 24 hours central Biochemistry Laboratory. Hypertension is considered here as blood pressure more than 140/90 mmHg. BP recorded on at least two occasions or with past history of systemic hypertension or ongoing treatment for systemic hypertension. Diabetes is considered here as fasting plasma glucose of ≥126 mg/dL or postprandial>200 mg/dL 2 hours after oral glucose load or random blood sugar level >200 mg/dL in symptomatic patients or history of receiving treatment for diabetes

mellitus or diagnosed in past as diabetes mellitus. Informed consent was obtained from both patients group and control group who participated in this study. The results were statistically analyzed with student t test , One Way ANOVA followed by TUKEY HSD test. The level of significance was considered if $p \leq 0.05$.

RESULTS

Eighty nine PD patients were studied of whom 21 (24%) were female and 68 (76%) were male as depicted in chart I.

Chart I depicting percentage of male and female PD patients



Among 89 patients,23 Patients{25.84%} (22-M; 1- F) belonged To Stage I; 32 Patients {35.95% }(30-M; 2- F) belonged To Stage II; 22 Patients{24.72% } (11-M; 11- F) belonged To Stage III ; and 12 Patients [13.48% } (5-M; 7- F) belonged To Stage IV based on Modified Hoehn And Yahr staging as per table I.

Table I showing number of PD patients in each stage

STAGING	MALES	FEMALES	TOTAL
STAGE I	22	1	23
STAGE II	30	2	32
STAGE III	11	11	22
STAGEIV	5	7	12
TOTAL	68	21	89

The mean serum uric acid levels in male PD patients was 5.406 while in controls it was 6.471 which is statistically significant. The mean serum uric acid levels in females PD patients was 4.757 in while in controls it was 6.186 a statistically significant value as depicted in chart II. The mean serum uric acid levels in all PD patients was 5.253 while in controls it was 6.403 which is also statistically significant indicating those having low serum uric acid level are at significant risk of PD [Table II & Chart III].

Table II showing mean uric acid levels in controls and patients in both sexes

MEAN URIC ACID LEVELS	CONTROLS	PATIENTS	P VALUE
MALES	6.471	5.406	<0.001
FEMALES	6.186	4.757	<0.001
TOTAL	6.403	5.253	<0.001

Chart II showing mean uric acid levels in controls and patients in both sexes

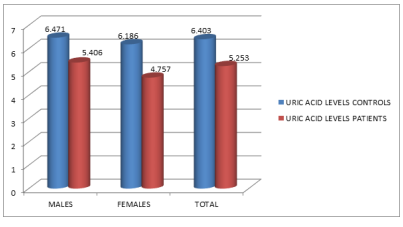
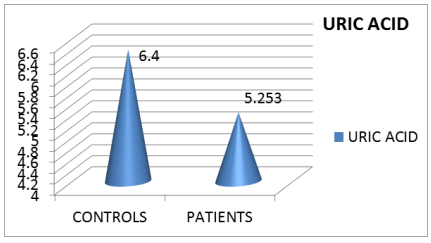


Chart III illustrating Mean uric acid levels in controls and patients



The mean serum uric acid levels in PD patients in stage I was 5.865; stage II was 5.394; Stage III was 4.882 and Stage IV was 4.382 [Table III]. As stage worsens mean serum uric acid level is also is declining indicating reduced serum uric acid level is associated with more severity of PD [8,9][Chart IV].

Table III showing stage wise mean uric acid level

MEAN URIC ACID LEVELS	MALES	FEMALES	0VERALL
STAGE I	5.864	5.9	5.865
STAGE II	5.390	5.450	5.394
STAGE III	4.99	4.773	4.882
STAGE IV	4.40	4.371	4.383

Chart IV depicting decrease in mean uric acid level as stage of PD worsens

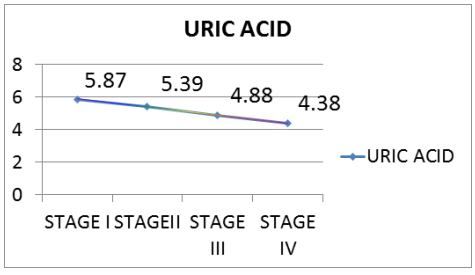
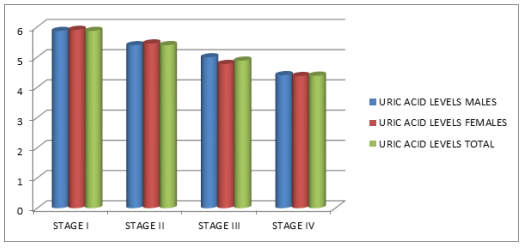


Chart V depicting decrease in mean uric acid level as stage of PD worsens in both sexes



Average uric acid levels based on duration of PD was 5.87 in 3.7 years ; 5.39 in 6.82 years , 4.88 in 8.7years and 4.38 in 10.5 years[Chart V]. Serum uric acid levels tends to decrease as the PD duration increases[8,9][CHART VI, VII].

CHART VI depicting decrease in uric acid levels duration of PD increases

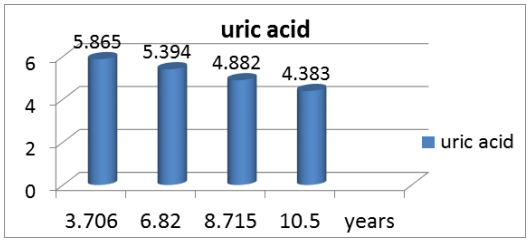
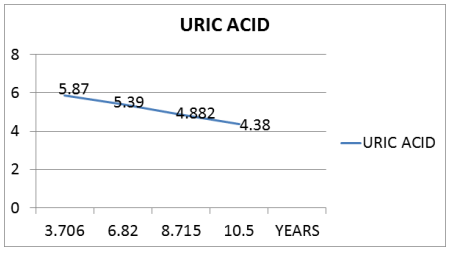


Chart VII Depicting Decrease Of Uric Acid Levels As PD Duration Increases



DISCUSSION

There are many studies substantiating the people with elevated serum uric acid level have a decreased incidence of idiopathic PD[10,11]. In 1996, Davis et al. in the Honolulu Heart Program had described that, men with uric acid levels more than median was found to have 40

percent reduction in the incidence of PD. Studies showed the increased incidence of Parkinson's disease and morbidity due to disease progression when the uric acid level was low [12]. Andreadou et al in his study has shown reduced uric acid levels in the serum of PD patients. Also low uric acid level were found to have an increased risk of PD [13] consistent to our study. Serum uric acid is significantly reduced in PD when compared to controls. It correlates significantly with Modified Hoehn And Yahr Staging and duration of illness. The first prospective study of urate and the risk of PD demonstrated that, among some 8000 Japanese–American men (with a median age of 54 years at enrollment) in the Honolulu Heart Program, of the 92 individuals who developed PD, those who had a baseline serum urate level above the median had a 40% reduction in their rate of idiopathic PD incidence over the ensuing 30 years (rate ratio: 0.6; 95% CI: 0.4–1.0); analysis was adjusted for age and smoking [14,17]. Identical results were found in the Rotterdam Study, a prospective population-based study of 4695 men and women, aged 55 years and older, without PD and dementia [15,17]. Within 9.4 years of follow-up sixty eight new cases of PD were detected. The results were normalized for sex, age, smoking, consumption of dairy products, BMI and alcohol intake. Higher serum level of uric acid was associated with a significant decreased risk of PD (hazard ratio [HR]: 0.71%; 95% CI: 0.51–0.98), with evidence of a dose–effect relationship (p-value for the trend = 0.040). Weisskopf *et al.* in the largest prospective study to date, analyzing blood sample data of 18,018 men who participated in the Health Professionals Follow-up Study and provided blood samples between 1993 and 1995 [16,17]. Between the period of blood collection and 2002, 84 subjects were diagnosed with PD. Analysis adjusted for age, smoking history and caffeine intake demonstrated that the risk of PD decreased across increasing urate quartiles. The mean plasma urate concentration was significantly lower among cases compared with Milk and meat consumption as well as exercise modify the risk of developing PD possibly through their influence on SU levels.In addition to meat, alcohol and fructose have been demonstrated to increase blood uric acid levels, whereas milk products have been found to reduce them. It is possible that a high purine diet in patients with PD may slow progression of PD[18]. Gao *et al.* reported that a composite index of such dietary factors predictive of higher plasma uric acid levels also predict a reduced risk of developing PD [19]

CONCLUSION

Although uric acid can act as an antioxidant, excess serum accumulation is often associated with cardiovascular disease [20,21]. It is not known whether this is causative (e.g., by acting as a prooxidant) or a protective reaction taking advantage of urate's antioxidant properties. The same may account for the putative role of uric acid in the etiology of stroke.Uric Acid is a double edged weapon. High serum uric acid may result in increased cardiovascular and cerebrovascular events. Low serum uric acid level may cause Parkinson's disease. So larger studies are required to find out optimum level of uric acid level to prevent both events . This study provides an association between uric acid levels and reduced occurrence of PD and its inversely relation to staging and duration of illness. Hyperuricemia acts as a neuroprotective marker from PD. Reduction in uric acid level is associated with increased risk of Parkinson's disease[PD]. Diet modification, iron, zinc supplements increase uric acid; their role in preventing and reducing the morbidity of PD to be confirmed with larger studies.

Grant Support: NIL.
Conflicts of Interest: NIL.

Institution Where Work was Performed

Institute of Neurology, Government medical college hospital, Madras Medical College Chennai Tamil Nadu, India.

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