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Relationship between Uric Acid Levels and Progressive Supranuclear Palsy (PSP)

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Abstract

Background—The pathophysiology of both Parkinson's disease (PD) and progressive supranuclear palsy is characterized by a pro-oxidant state. Uric acid is an oxidative stress marker. High uric acid blood levels have been associated with a reduced risk of PD and a decreased rate of disease progression. We investigated whether a low serum concentration of uric acid is also associated with progressive supranuclear palsy.

Methods—We measured serum uric acid concentrations in a subsample of the ENGENE progressive supranuclear palsy Cohort that included 75 cases and 75 frequency-matched-by-sex healthy controls (69 spouses, 6 in-laws) from 4 centers willing to participate (Case Western, Rush University, University of Utah, and University of Louisville). Case severity was characterized using the total progressive supranuclear palsy-Rating Scale, Unified PD Rating Scale and Mattis Dementia Rating Scale. Unconditional logistic regression, Pearson's chi-squared test and Analysis of Variance were used as appropriate.

Results—The mean uric acid level among cases (4.0 mg/dl) was not significantly lower than that of controls (4.1 mg/dl). When controlling for sex, there were no between-group statistical differences in uric acid levels. Uric acid levels were not correlated with disease severity.

Conclusion—The results of this study do not provide evidence of uric acid having a protective role in progressive supranuclear palsy, even if oxidative injury is important in the pathophysiology of this disorder. The lack of statistical significance suggests that there is no direct association

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between uric acid levels and progressive supranuclear palsy. However, a small inverse association cannot be excluded.

Keywords

progressive supranuclear palsy; uric acid; epidemiology; case-control study

INTRODUCTION

Oxidative stress has been linked to dopamine cell neurodegeneration and is related to the susceptibility for developing Parkinson's disease (PD).[1] Several studies have found that uric acid levels significantly correlate with the severity of dopaminergic impairment in the striatum.[1, 2] High plasma urate concentrations are lower in PD than in controls,[3] and urate levels are related to the progression of PD.[4, 5] Thus, uric acid is an antioxidant that has a potential therapeutic role in PD.[6, 7] Oxidative stress has also been implicated in the pathophysiology of progressive supranuclear palsy (PSP).[8–13]

PSP is the most common atypical parkinsonian disorder. Unlike PD, it clinically presents with early postural instability, supranuclear vertical gaze palsy, dysarthria, dysphagia, frontal cognitive disturbances and unresponsiveness to levodopa. There are no proven treatments to slow disease progression, and the prognosis of PSP is poor as survival is approximately 5–7 years.[14]

Currently, no study has investigated the relationship between uric acid and PSP.[3] We hypothesized that low uric acid levels could be associated with a greater risk of PSP and disease severity. We conducted a case-control study to determine if serum uric acid levels in PSP are lower than in healthy controls, and if there is a an association between uric acid levels and disease severity.

MATERIALS AND METHODS

Study population

This case-control study is a subsample from the ENGENE PSP cohort that included 350 cases with PSP, 301 controls matched on sex and age, and 283 spousal controls from 15 centers across North America. The present study was conceived after the ENGENE project had started and was unfunded. Therefore, not all sites chose to participate and we only included samples of subjects after the ENGENE study had started. The NIH did fund the recruitment of cases and controls as part of the ENGENE study. The study included 75 out of the 350 cases and 69 out of the 283 spousal controls and 6 out of the 301 matched controls from four out of the 15 centers accepting to participate in this study (Case Western Reserve University, Rush University Medical Center, University of Utah, and University of Louisville). The research study was approved by the IRB at each site.

In the ENGENE study, spousal controls were matched on age and had no parkinsonism or dementia according to the validated Telephone Interview of Cognitive Status (TICS-M, *score* ≥ *28*) [15] and the Telephone Questionnaire for PD.[16] Cases met NINDS-SPSP diagnostic criteria [17] and were diagnosed with PSP within the previous year by the screening

site principal investigator. Subjects were excluded if they presented confounding medical factors. All subjects were interviewed over the phone by members of the central site team using the Stewart questionnaire.[18] This included questions regarding educational level, use of medications, exposure to chemicals, alcohol consumption and smoking.

Assessment of exposure

Blood samples of all subjects were drawn during site visits between 2008 and 2011 and centrifuged before being stored in the vapor phase of liquid nitrogen freezers. Tables 1 and 2 show the subjects characteristics at time blood was drawn. All site samples were sent at the same time to the central testing site. Uric acid levels were analyzed in one a single batch at LabCorp, using uricase methodology (enzyme-linked immunoassay). The coefficient of variation of the uric acid measurement was 1.1% (LabCorp). Sample testing was done in duplicate but LabCorp does not report the duplicate values.

Statistical analyses

The frequency of categorical characteristics between case and control groups was compared and tested using Pearson's chi-squared test, unless otherwise noted. The distribution of continuous variables between case and control groups was compared and tested using the t-test unless otherwise noted. Estimated odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression[19], unless otherwise noted. One-way Analysis of Variance (ANOVA) was used to compare the uric acid levels between the cases and controls. In order to compare the mean uric acid levels between genders, both One-way Analysis and contingency analysis were performed. A p-value of less than 0.05 (5%) was used to determine statistical significance.

RESULTS

Table 1 shows the demographics of both cases and controls in this study. There were no significant differences in age, gender or education. Table 2 shows the cognitive and neurological characteristics of the cases. The mean symptom duration among cases was 3.7 years, mean Total Unified Parkinson's disease rating scale (UPDRS) score was 43.5, and mean Total PSP rating scale (PSP-RS) score was 33.0, indicating moderate disability. Although general cognitive functioning was borderline impaired for the sample as a whole (DRS-2 Total score of 125.3), scores on the DRS-2 were highly affected by poor performance on the subscale most associated with executive functioning--DRS-2 Initiation/Perseveration. Table 3 shows the distribution of serum urate concentrations among cases and controls. The mean plasma urate concentration among cases (4.0 mg/dl, 3.6–4.4 mg/dl) was not significantly lower than that of controls (4.1 mg/dl, 3.6–4.5 mg/dl, p=0.74). When controlling for sex, there were no between-group statistical differences in urate levels (female cases: 3.8 mg/dl, 3.3–4.3 mg/dl, female controls: 3.4 mg/dl, 2.9–4.0 mg/dl, p=0.29; male cases: 4.1 mg/dl, 3.5–4.7 mg/dl, male controls: 4.7 mg/dl, 4.1–5.3 mg/dl, p=0.17). Uric acid levels were not statistically correlated with disease severity. There were no between-group differences in age, even when stratified by gender (Table 1). However, men had significantly higher uric acid levels than women, as expected (Table 3). When controlling for gender while determining if there is an association between uric acid levels and PSP using

multivariable unconditional logistic regression, we found that when males were used as a reference level, the p-value was 0.939 with an odds ratio of 0.98 and a 95% confidence interval 0.51 to 1.88. The uric acid levels of cases and controls were also determined using logistic regression, showing a p-value of 0.734 with an odds ratio of 0.97 and a 95% confidence interval of 0.80 to 1.17. For every 1-unit increase in uric acid, the odds of having PSP decreased by 3%.

Table 4 shows a lack of association between cases' uric acid levels and their neurological features.

Power Justification

For comparing a continuous outcome, using a two sample two-sided t test at alpha=0.05, with a sample size of 37 in each group (males), and a standard deviation of 1.8 in each group, we have 29.3% power to detect if the difference in means is at least 0.60 corresponding to a moderate effect size.[20] For a one-sided test with the same conditions as above, the power is 41%.

DISCUSSION

This case-control study examined the concentrations of uric acid in 75 patients with PSP and 75 age and gender-frequency-matched healthy controls. We found no between-group statistical differences in uric acid concentrations. In addition, we did not find any association between uric acid levels and the main motor and non-motor characteristics of PSP. Our results differ from those found in PD, even though oxidative stress is hypothesized to play a critical role in both conditions. However, these preliminary results do not exclude the detection of a small inverse relation between uric acid and PSP. In fact, the 0.6 mg/dL difference in uric acid levels in men is slightly higher than the difference that Weisskopf et al.[3] found between men with PD (5.7 mg/dL) and controls (6.1 mg/dL). [21] Given that there were normal controls with uric acid values outside the normal range established by the central lab, we searched for outliers using the Pearson residual statistics but did not find any. Since methodological lab errors were unlikely as all the samples were analyzed at the same time and by duplicate at a recognized lab, an alternative possibility that could explain failure to confirm our hypothesis is that this sample size was smaller than that included in previous PD studies. Since methodological lab errors were unlikely, as all the samples were analyzed at the same time and by duplicate design at a recognized lab, the remaining possibility as to why our hypothesis was not confirmed is the fact that this sample size was smaller than those in prior PD studies. Thus, in view of the moderate size of our study, we cannot rule out small effect sizes, but this study does not support the hypothesis that uric acid is associated with PSP in a similar manner as it is to PD.

A variety of environmental and genetic factors have been implicated in the pathogenesis of PD and related parkinsonian conditions. In the case of PD, clinical, epidemiological, and laboratory evidence has suggested that uric acid, an antioxidant and end product of purine metabolism, may be a predictor for both reduced risk and favorable progression of the disease. Uric acid is one of the most prevalent antioxidants in human blood; it comprises 60–70% of plasma.[22]

Similar to PD, multiple studies have suggested that oxidative stress plays a role in the pathogenesis of PSP, a distinct, but clinically related neurodegenerative disorder.[23] Studies have shown that certain oxidative products are increased in affected brain PSP areas. In fact, oxidative damage of the proteins phosphoglycerate kinase 1 (PGK-1) and fructose bisphosphate aldolase A (aldolase A) is markedly increased in the frontal cortex in PSP.[24] PSP is a tauopathy, with both cortical and subcortical aggregated tau proteins in which there are aberrant post-translational modifications and fibril formation of these “primary” proteins. This may prevent degradation and lead to cellular and extracellular accumulation.[25] It is hypothesized that genetic factors, neurotoxins, environmental factors and primary oxidative damage all contribute to tau deposition in affected areas.

Our study did not find significant correlation between urate levels and disease severity, which may suggest a lack of an association with disease progression. Unlike those with PD, we found that patients with PSP did not have reduced levels of uric acid when compared with controls. This finding raises questions whether oxidative damage plays a major role in the neurodegenerative process in PSP. In this case, normal or high uric acid levels would confer no advantage in reducing PSP risk or ameliorating the condition.[26]

One possible explanatory mechanism is that neurodegenerative changes in PSP may allow urate to preferentially enter damaged cells. There could be several membrane effects that would allow this to occur. In plasma, urate functions as an antioxidant. Within the cell, however, it functions as a pro-oxidant; this may explain why high or normal urate levels would not offer any advantage in reducing PSP risk or ameliorating its clinical progression.[26] In diseases with extensive oxidative damage, such as hypertension, diabetes, and coronary artery disease, uric acid levels may rise as a secondary phenomenon. If the same effect occurred with PSP, then uric acid would not be expected to be decreased when compared with unaffected individuals.[26] Another possibility is that neural tissue in PSP may produce less oxidative damage and free radical formation than in PD. Thus, high or normal levels of uric acid would not be needed to reduce this low level of oxidative stress. Consequently, urate would not play a major protective role in PSP. Conversely, in this case lower uric acid levels would not be expected to be associated with a higher incidence of disease.[26] Many neurodegenerative disorders are associated with oxidative stress, but it is possible that urate plays a unique role only in PD.

It has been found that the endogenous antioxidant system of PSP patients is activated with aging, but it may be unable to function effectively because of conjugation with 4-hydroxynonenal (HNE).[23] It is also possible that other antioxidant agents besides uric acid may play a role in PSP risk and progression. Ongoing PSP studies are evaluating the effects of coenzyme Q10; future studies could test the effects of magnesium and other related substances.

This study has limitations, including possible misdiagnosis of clinical cases. This has been minimized by employing expert movement disorder specialists to diagnose these patients using the NINDS-SPSP criteria, which have been shown to have high specificity and positive predictive value.[27] A larger study population, or the addition of more controls, would have allowed for detecting a smaller size effect. However, since the technology

currently employed to test uric acid differs from that used when the study was conducted results would not be comparable. Another limitation is not having controlled for factors affecting uric acid levels such as body mass index, diet, creatinine levels and use of diuretics. Additionally, we cannot rule out other unknown confounding factors.

In summary, we did not find an association between serum urate levels in patients with PSP and the urate levels in controls, but further research is warranted to test other antioxidant mechanisms.

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Table 1

Subjects Demographics

	Group			
Variable	**Total (n=150)**	**PSP Cases (n=75)**	**Control (n=75)**	**P Values**
Age				
Group age (yrs)	67.1 ± 7.8	67.5 ± 6.7	66.7± 7.8	0.467
Female age (yrs)	66.1 ± 7.5	67.2 ± 6.9	65.0 ± 7.9	0.194
Male age (yrs)	68.1 ± 6.9	67.8 ± 6.6	68.4 ± 7.4	0.741
Gender				1.00
Female N (%)	76 (50.6)	38 (25.3)	38 (25.3)	
Male N (%)	74 (49.3)	37 (24.7)	37 (24.7)	
College				0.322
Diploma				
Yes (%)	86 (57.3)	40 (53.3)	46 (61.3)	
No (%)	64 (42.7)	35 (46.7)	29 (38.7)	

yrs = years; n = number.

Table 2

Distribution of Cases Characteristics

Cases features	
Disease Duration (Years)	
Mean (95%CI)	3.7 (3.4 – 3.9)
Median (min – max)	4.0 (1.0 – 8.0)
UPDRS Total	
Mean (95%CI)	43.5 (40.5 – 46.6)
Median (min – max)	42.0 (17.0 – 76.0)
PSP-RS Total	
Mean (95%CI)	33.0 (30.8 – 35.2)
Median (min – max)	31.0 (17.0 – 60.0)
MDRS Total	
Mean (95%CI)	125.3 (123.0 – 127.7)
Median (min – max)	126.0 (101.0 – 141.0)

UPDRS = Unified Parkinson Disease Rating Scale; PSP-RS = PSP Rating Scale; MDRS = Mattis Dementia Rating Scale

Table 3

Uric Acid Levels in Cases and Controls

	Group			
Uric Acid	**Total (n = 150)**	**Case (n = 75)**	**Control (n = 75)**	**P Value**
				0.742
Mean (95%CI)	4.0 (3.7 – 4.3)	4.0 (3.6 – 4.4)	4.1 (3.6 – 4.5)	0.740 *
Median (min – max)	4.1 (0.4 – 9.4)	4.0 (0.4 – 9.4)	4.2 (0.7 – 8.4)	
Females				0.286
Mean (95%CI)	3.6 (3.3 – 4.8)	3.8 (3.3 – 4.3)	3.4 (2.9 – 4.0)	0.283 **
Median (min – max)	3.8 (0.4 – 6.6)	4.0 (0.4 – 6.6)	3.4 (0.7 – 6.4)	
Males				0.167
Mean (95%CI)	4.4 (4.0 – 4.8)	4.1 (3.5 – 4.7)	4.7 (4.1 – 5.3)	0.167 **
Median (min – max)	4.6 (1.2 – 9.4)	4.2 (1.3 – 9.4)	4.7 (1.2 – 8.4)	
		Female	**Male**	
Cases and Controls		n = 76	n = 74	0.006
Mean (95%CI)		3.6 (3.3 – 4.8)	4.4 (4.0 – 4.8)	
Median (min – max)		3.8 (0.4 – 6.6)	4.6 (1.2 – 9.4)	
Only Cases		n = 38	n = 37	0.455
Mean (95%CI)		3.8 (3.3 – 4.3)	4.1 (3.5 – 4.7)	
Median (min – max)		4.0 (0.4 – 6.6)	4.2 (1.3 – 9.4)	
Only Controls		n = 38	n = 37	0.002
Mean (95%CI)		3.4 (2.9 – 4.0)	4.7 (4.1 – 5.3)	
Median (min – max)		3.4 (0.7 – 6.4)	4.7 (1.2 – 8.4)	

P-Values from chi-squared test for categorical variables and from t-test for continuous variables;

* P-values from conditional logistic regression.

** P-values from unconditional logistic regression.

n = number.

Table 4

Association between cases uric acid levels and their neurological features

Features	Estimate*	95% CI*		R^2	P**	P***
UDPRS Total	0.369	−1.482	2.220	0.002	0.692	0.754
PSP-RS Total	0.211	−1.130	1.552	0.001	0.755	0.771
MDRS Total	−0.491	−1.893	0.911	0.007	0.488	0.489

CI = Confidence interval;

*All estimates and 95% CI are for uric acid, the explanatory variable; P** = P-Value for uric acid, univariable linear regression model; P*** = P-Value for uric acid in multivariable linear regression model adjusted for gender; R^2 = square of Pearson correlation coefficient. UPDRS = Unified Parkinson Disease Rating Scale; PSP-RS = PSP Rating Scale; MDRS = Mattis Dementia Rating Scale.