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Serum urate and probability of dopaminergic deficit in early ‘Parkinson disease’

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Abstract

Objective—Investigate whether higher levels of urate, an antioxidant linked to a lower likelihood of developing Parkinson disease (PD), is also a predictor of having a dopamine transporter brain scan without evidence of dopaminergic deficit (SWEDD).

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Dr. Marek is a consultant/AD board member for GE Healthcare, Alseres, EMD Serono, Lilly, Bayer Healthcare, Sanofi, and Biogen. He has ownership interest in Molecular NeuroImaging, LLC. Dr. Seibyl is a consultant/AD board member for Bayer Healthcare, GE Healthcare, and Neurologica. He has equity interest in Molecular NeuroImaging, LLC.

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Methods—In a cross-sectional study of 797 mildly affected, untreated parkinsonian subjects diagnosed with early PD in the Parkinson Research Examination of CEP-1347 Trial (PRECEPT), we investigated the relationship at baseline between serum urate and striatal dopamine transporter density, determined by single-photon emission computed-tomography of iodine-123-labeled 2- β -carboxymethoxy-3- β -(4-iodophenyl)tropane ([123 I] β -CIT) uptake. A SWEDD was defined as lowest putamen [123 I] β -CIT > 80% age-expected putamen DAT density.

Results—Odds of having a SWEDD rose across increasing quintiles of urate level, with an age- and gender-adjusted odds ratio of 3.2 comparing the highest to the lowest urate quintile; 95% CI: 1.5 to 7.2; p for trend = 0.0003) and remained significant after adjusting for potential confounding factors. The association was significant in men but not women, regardless of whether common or sex-specific quintiles of urate were used.

Conclusions—Higher levels of urate were associated with a greater likelihood of a SWEDD amongst subjects with early untreated parkinsonism in the PRECEPT study. The findings support the diagnostic utility of urate in combination with other determinants.

Keywords

Parkinson disease; urate; dopamine transporter; neuroimaging; diagnosis; biomarker

INTRODUCTION

Urate is a potent antioxidant¹ and may reduce the oxidative damage suspected to contribute to the neurodegenerative process in Parkinson disease (PD).^{2, 3} Consistent with this hypothetical benefit, individuals with higher levels of serum urate have been consistently found to have a decreased risk of PD in several longitudinal studies.^{4–7} Similarly, dietary⁸ and genetic⁹ determinants of higher serum urate recently have been linked to a reduced risk of PD or a later age at onset. These studies, however, relied on clinical diagnoses of PD, and some level of diagnostic misclassification is likely. Randomized clinical trials targeting early PD and conducting dopaminergic imaging may provide an attractive complementary opportunity to investigate potential effects of serum urate on PD risk. Approximately 10% of the participants in these trials have a scan without evidence of dopaminergic deficit (SWEDD),^{10–13} and may not have PD, as suggested by the lack of disease progression and often by a revision of the clinical diagnosis at the end of the trial.^{10, 14} These subjects therefore constitute a useful control group for case-control studies of risk factors for PD in which the cases are those subjects with evidence of dopaminergic deficit recruited in the same trial -- if individuals with higher urate levels have a decreased risk of PD, the probability of a SWEDD would be expected to be higher in patients with higher urate.

We therefore examined cross-sectionally the relation between baseline serum urate concentrations and baseline imaging results among participants enrolled in the Parkinson Research Examination of CEP-1347 Trial (PRECEPT), a large randomized clinical trial that was originally designed to investigate a candidate neuroprotectant in PD using clinical and imaging assessments of disease progression due to continued neurodegeneration.¹³

METHODS

Study population

The PRECEPT study was carried out by the Parkinson Study Group, and sponsored by Cephalon, Inc. and H. Lundbeck A/S. The participants ($n=806$) were enrolled between April 2002 and April 2004 at 65 sites across the United States and Canada. All participating sites obtained approval of the protocol by their institutional review boards, and all subjects gave written consent for study participation. The present study was conducted on the data for all

PRECEPT subjects with serum urate values and functional neuroimaging results at baseline. As previously described, subjects to be enrolled in the study had to have a diagnosis of early PD (modified Hoehn and Yahr stage of ≤ 2.5 with two of the cardinal signs: resting tremor, bradykinesia or rigidity) and no current or imminent (in the next 3 months) disability requiring dopaminergic therapy.¹³ Exclusion criteria included atypical parkinsonism, a diagnosis of PD ≥ 5 years duration, a tremor score ≥ 3 , a Mini-Mental Status Exam score ≤ 26 , a Beck Depression Inventory score ≥ 15 or the use of symptomatic therapy within six months prior to randomization. Subjects were randomly assigned to receive placebo or CEP-1347 10 mg, 25 mg, or 50 mg twice daily.

Serum urate and covariates

Serum urate was measured at screening as well as the subsequent baseline visit (on average 4 weeks apart) as one component of the routine safety monitoring performed. The correlation between the screening and baseline serum urate was high ($r=0.88$; $p<0.0001$), and only baseline values, which were available for 99.8% of patients enrolled in the trial, have been used in the present analyses. Serum urate levels in blood samples drawn under non-fasting conditions were determined using an enzymatic assay performed at a central commercial clinical laboratory (Covance, Indianapolis, IN). Information on past medical history and regular use of medications was collected at the screening visit.

Neuroimaging

Single-photon emission computed-tomography (SPECT) of iodine-123-labeled 2- β -carboxymethoxy-3- β -(4-iodophenyl)tropane ($[^{123}\text{I}]\beta\text{-CIT}$) uptake was used at baseline to measure striatal dopamine transporter density among all subjects in the trial; imaging was carried out at the Institute for Neurodegenerative Disorders in New Haven, Connecticut with methods as described previously.¹⁵ Based on a previously acquired database of 100 healthy subjects, baseline scans were categorized as DAT deficient ($\leq 80\%$ age-expected lowest putamen $[^{123}\text{I}]\beta\text{-CIT}$), or not DAT deficient ($> 80\%$ age-expected lowest putamen $[^{123}\text{I}]\beta\text{-CIT}$).¹⁶

Statistical analysis

The relation between serum urate at baseline and SWEDDs was assessed by logistic regression, adjusting for age and gender. Initial analyses were conducted using quintiles based on the combined urate distribution in men and women ("common quintiles"). An important advantage of using common quintiles is that the odds ratios in men and women estimate the effects of similar levels of serum urate. However, because of the expected higher level of urate in men, this categorization resulted in a markedly skewed distribution within gender, with mostly men in the top quintiles and mostly women in the bottom quintiles of serum urate, and thus in a loss of power of analyses within gender. These analyses were therefore complemented by estimating odds ratios for gender-specific quintiles. Tests for trend were conducted by including serum urate as a continuous variable in the logistic regression models (Wald test). Potential confounding was assessed by adjusting the regression analyses for body mass index (continuous), smoking (current smoking vs past or never), history of hypertension, history of high cholesterol, use of non-steroidal anti-inflammatory drugs, and use of thiazides. Possible interaction between serum urate and gender was explored by including in the logistic regression model the cross-product of serum urate as a continuous variable with gender.

All the p values presented are for 2-tailed tests with levels < 0.05 defined as significant.

RESULTS

Serum urate values and SPECT β -CIT imaging at baseline were available for 797 patients, including 90 classified as having SWEDDs (Table 1). Selected characteristics of these subjects according to imaging results are shown in Table 1.

In analyses using quintiles of serum urate in men and women combined, the odds of a patient having a SWEDD increased with increasing urate levels (age- and gender-adjusted OR comparing the highest to the lowest urate quintile = 3.2; 95% CI: 1.5 to 7.2; p for trend = 0.0003) (Table 2). The trend of increasing odds of a SWEDD with increasing urate remained strong and significant after simultaneous adjustment for body mass index, smoking, history of hypertension, history of high cholesterol, use of non-steroidal anti-inflammatory drugs, and use of thiazides (p for trend = 0.01). The association was stronger in men than in women, although a test of interaction between serum urate (as a continuous variable) and gender was not significant ($p=0.3$). Because of the marked difference in serum urate levels between men and women, we also conducted analyses based on gender-specific quintiles of serum urate. Results were similar to those using common quintiles – among men, high serum urate was strongly associated with the odds of being a SWEDD, whereas a weaker and non-significant association was found in women (Table 3).

DISCUSSION

Urate, a major antioxidant as well as the end product of purine metabolism in humans, has emerged as a biomarker of PD at multiple stages of the disease process.¹⁷ Specifically, prior to diagnosis lower serum urate indicates an increased risk of the disease becoming clinically manifest years later.^{4–7} Shortly after symptoms have developed, urate can serve as a prognostic biomarker with lower serum or CSF levels foretelling a greater likelihood of faster disability progression,^{18, 19} or of faster loss of dopamine transporter binding sites in striatum¹⁵. The current findings demonstrate the potential diagnostic relevance of serum urate early in clinically manifest disease. They do so by identifying amongst those with mild parkinsonism a significant correlation between lower serum urate and reduced striatal uptake of a dopamine transporter ligand in a pattern indicative of idiopathic PD because of its characteristic deficit of nigrostriatal dopaminergic innervation. Conversely, higher – but still normal – levels of urate were linked to SWEDDs and thus to a lesser likelihood of having true PD.

The correlation between urate and SWEDD status was robust in men but unclear in women. This apparent gender difference parallels similarly strong links between urate and PD risk or its progression^{18, 19} in men more than women. The gender difference in urate correlations may represent a true biological difference between men and women. Alternatively, the lack of significance for women might simply reflect the much smaller (here 6-fold compared to men) contribution of women to the highest two urate quintiles because of naturally lower levels of urate in women as well as the smaller number of women enrolling in PRECEPT.

Although higher serum urate amongst subjects recently diagnosed with ‘PD’ may be indicative of an alternative diagnosis, urate as biomarker of PD is not sufficiently specific on its own to distinguish PD and non-PD diagnoses. Nevertheless it may be combined with other diagnostic biomarkers to form a more useful composite indicator of non-PD diagnoses in early parkinsonism. In addition to SWEDD status, preserved olfaction has recently been substantiated as a potentially practical indicator of a non-PD diagnosis amongst newly diagnosed parkinsonian patients. It has been proposed that olfactory test performance, which has also been associated with SWEDDs in early parkinsonism,²⁰ in combination with distinctive PD motor features (e.g., asymmetric rest tremor²¹) may serve as a more

accessible and less expensive diagnostic biomarker compared to this functional neuroimaging technique. Thus it will be conceptually informative and possibly clinically useful to combine multiple readily available, simple tests – e.g., of serum urate and olfactory function – to determine how the diagnostic value (i.e., of higher urate and preserved olfaction) compares to that with either test result alone. Similarly, a crude composite index of suspicion for a non-PD diagnosis may aid in triaging subjects for more incisive diagnostic assessment with DAT neuroimaging.²²

Amongst subjects diagnosed with early PD in the PRECEPT¹⁸ and DATATOP¹⁹ trials, those with higher levels of serum urate were found to decline clinically and radiographically at a slower rate than those with lower urate levels. The current findings suggest that at least some of urate's capacity as a prognostic biomarker amongst those newly diagnosed with PD can be explained by the higher proportion of SWEDDs amongst 'early PD' subjects with higher urate levels. Because SWEDD subjects show little evidence of clinical and radiographic progression for at least 2–4 years from baseline,^{10, 11, 20, 23, 24} their greater representation amongst those with higher urate likely contributed to the relatively favorable prognosis observed amongst those with a PD diagnosis and higher urate levels.^{18, 19} However, the urate-SWEDD link could only partially account for the predictive association between higher urate at baseline and slower clinical progression because the association remains strong even after excluding all 90 subjects with a baseline SWEDD from a secondary analysis of the PRECEPT cohort¹⁸ (unpublished observations, AA, KM, A. Watts, SE, IS, MAS). Specifically, the HR for reaching the endpoint still declined with increasing serum urate in analyses including men and women combined ($p=0.002$ for trend) with the an HR of 0.61 for those in the highest versus the lowest serum urate quintile (95% CI: 0.43 to 0.86; $p=0.005$). As before,¹⁸ the HR reduction was even greater and more significant in men and was absent in women. Similarly, the reported¹⁸ predictive association between higher baseline urate and slower decline in striatal β -CIT uptake persisted after excluding those with a baseline SWEDD from analysis, and though diminished it remained statistically significant amongst men.

Accuracy in the diagnosis of PD early in the course of parkinsonian conditions is of considerable importance for clinical research as well as for prognostic counseling.²⁵ Although experience and specialization in movement disorders neurology appears to improve the positive predictive value of an idiopathic PD diagnosis to nearly 99% based on definitive pathological assessment,²⁶ this high level of probability was achieved only after following patients who presented with parkinsonism for five years on average before diagnostic revision. Diagnostic accuracy is naturally lower early in the course of parkinsonian conditions when symptoms are fewer and subtler and when responsiveness to dopaminergic drug therapy – an important diagnostic indicator in PD – has not yet been assessed. However, this early so-called *de novo* clinical phase of the disease has traditionally been the focus of therapeutic trials investigating potentially neuroprotective agents. Thus, it is not surprising that such clinical trials enroll a significant percentage of parkinsonian subjects who ultimately receive a diagnosis other than PD, for example, with 7% of the 800 subjects in the DATATOP trial who were initially thought to have PD upon enrollment being later deemed no longer likely to have the disease.¹⁴ In several more recent trials also investigating potentially disease-modifying agents in *de novo* PD a similar proportion (~10%) of subjects have been identified as possibly not having PD, though in these studies the evidence was available at baseline when functional brain scans unexpectedly showed normal labeling of dopaminergic innervation in the striatum, i.e., SWEDDs. The demonstration that higher urate is a predictor of SWEDD status suggests that urate may be useful as a component of a composite diagnostic indicator early in the course of parkinsonian conditions. The findings broaden the diagnostic biomarker potential of urate in

PD, and lend further support to the possibility of a role for urate in the pathophysiology of the disease and its future treatment.

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Table 1

Baseline characteristics by gender and SWEDD status

	Females		Males	
	SWEDD (n=45)	DAT Deficit (n=242)	SWEDD (n=45)	DAT Deficit (n=465)
Age at Enrollment	59.0 (12.6)	59.6 (9.9)	59.5 (14.3)	59.7 (9.7)
Serum Uric Acid	4.9 (1.6)	4.6 (1.3)	6.7 (1.4)**	6.0 (1.3)
Total Cholesterol	207 (31)	210 (34)	194 (41)	195 (36)
Body Mass Index (BMI)	27.7 (6.2)	26.4 (5.2)	29.7 (3.9)**	27.8 (4.2)
Total UPDRS	19.2 (7.3)***	25.4 (10.9)	18.3 (9.7)***	25.4 (10.3)
MMSE	29.2 (1.0)	29.4 (0.9)	28.8 (1.1)**	29.3 (1.0)
Use Antihypertensive Drugs	16 (36%)	80 (33%)	18 (40%)	164 (35%)
Use NSAIDs	10 (22%)	75 (31%)	12 (27%)	121 (26%)
Use Thiazides	7 (16%)	27 (11%)	6 (13%)	42 (9%)
Current Smoker	3 (7%)	15 (6%)	6 (13%)	33 (7%)

Mean (SD) or N (%), as appropriate.

*
p <0.05;**
p<0.01;***
p<0.001 compared (within gender) to those with a DAT deficit.

Table 2

Odds ratios (OR) of SWEDD status at baseline according to common quintiles of serum urate, adjusted for age group and gender.

	All			Female			Male				
Serum urate quintile (mg/dL)	N	OR (95% CI)	P-value	N	with a SWEDD	OR (95% CI)	P-value	N	with a SWEDD	OR (95% CI)	P-value
Q1: <=4.3	177	1 (Reference)	-	132	14%	1 (Reference)	-	45	2%	1 (Reference)	-
Q2: >4.3-5.1	156	1.4 (0.7, 3.1)	0.35	70	11%	1.1 (0.4, 2.8)	0.87	86	8%	4.3 (0.5, 39.5)	0.20
Q3: >5.1-5.8	146	1.1 (0.4, 2.7)	0.85	37	16%	1.6 (0.5, 4.7)	0.39	109	3%	1.4 (0.1, 15.1)	0.80
Q4: >5.8-6.7	167	2.5 (1.1, 5.5)	0.023	26	31%	2.6 (0.9, 7.4)	0.08	141	10%	5.4 (0.6, 48.0)	0.13
Q5: >6.7	151	3.2 (1.5, 7.2)	0.0037	22	18%	1.7 (0.4, 6.1)	0.45	129	16%	9.4 (1.1, 81.0)	0.04
P-value for trend			0.0003				0.051				0.0009

Table 3

Odds ratios (OR) of SWEDD status at baseline according to gender specific quintiles of serum urate, adjusted for age group.

	Female				Male			
Serum urate quintile level	Serum Urate	with a SWEDD	OR (95% CI)	P-value	Serum Urate	with a SWEDD	OR (95% CI)	P-value
Q1	≤3.7	16%	1 (Reference)	-	≤4.9	4%	1 (Reference)	-
Q2	>3.7-4.2	13%	1.1 (0.3, 3.6)	0.88	>4.9-5.6	7%	2.1 (0.5, 8.5)	0.27
Q3	>4.2-4.8	11%	1.1 (0.3, 3.7)	0.88	>5.6-6.3	9%	2.7 (0.7, 10.0)	0.15
Q4	>4.8-5.6	12%	1.2 (0.4, 4.0)	0.73	>6.3-7.0	7%	2.1 (0.5, 8.4)	0.30
Q5	>5.6	27%	2.6 (0.9, 7.8)	0.08	>7.0	18%	6.8 (1.9, 23.8)	0.0028
P-value for trend				0.051				0.0009