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The Relationship between Uric Acid Levels and Huntington's Disease Progression

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Abstract

Uric acid (UA) may be associated with the progression of Parkinson's disease and related neurodegenerative conditions; however, its association with Huntington's disease (HD) progression has not been explored. A secondary analysis of 347 subjects from the CARE-HD clinical trial was performed to examine the relationship between baseline UA levels and the level of functional decline in HD. Outcomes included change in scores at 30 months for the Unified Huntington's Disease Rating Scale components. There was less worsening of total functional capacity over time with increasing baseline UA levels (adjusted mean worsening in scores: 3.17, 2.99, 2.95, 2.28, 2.21, from lowest to highest UA quintile, p=0.03). These data suggest a possible association between higher UA levels and slower HD progression, particularly as measured by total functional capacity. If confirmed, UA could be an important predictor and potentially modifiable factor affecting the rate of HD progression.

Keywords

Huntington's disease; uric acid; progression

Introduction

Uric acid (UA) is a known antioxidant with greater blood concentrations found in humans compared to shorter-lived mammals, suggesting an evolutionary benefit.1 UA is a scavenger of oxygen radicals, and oxidative damage has been hypothesized to contribute to aging and neurodegeneration.2 Higher UA levels may serve a potential therapeutic role against oxidative damage associated with neurodegenerative diseases.

Studies suggest that UA could be a novel target for neuroprotective therapies. UA has been found to be protective in reducing brain injury after ischemic stroke.3 Lower serum UA concentrations have been found in persons with Alzheimer's disease compared to healthy controls and persons with higher UA levels have been shown to have a lower risk of

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developing Parkinson's disease (PD).[4,5] In addition, UA concentrations have been found to be reduced in Huntington's disease (HD) as compared to controls in several regions of the cerebral cortex.[6]

Higher UA concentrations have been linked to slower clinical progression of PD among those with early PD.[7] It is plausible that this association may also exist with other neurodegenerative diseases such as HD, and that serum UA may be a potential biomarker of clinical progression in HD. The objective of this study was to examine the relationship between baseline UA levels and the level of functional decline in HD patients over a 30 month period.

Methods

The Co-Enzyme Q_{10} and Remacemide: Evaluation in Huntington's Disease (CARE-HD) clinical trial was the source of data for this study.[8] This was a multicenter, randomized, double-blind, parallel group clinical trial conducted during July 1997– February 2002. The 347 participating subjects were randomized to receive either coenzyme Q_{10} (600 mg/day), remacemide (600 mg/day), both treatments, or matching placebo and were evaluated with clinical assessments over a 30 month period. Subjects had a confirmatory CAG repeat expansion (≥39) consistent with HD, early HD defined as stages I or II of illness (total functional capacity (TFC) ≥7), and were 14 years of age or older. Subjects were excluded if there was clinical evidence of unstable medical or psychiatric illness, history of serious alcohol or drug abuse within the preceding year, use of any investigational drug within 30 days of the study, or use of coenzyme Q_{10} or remacemide in the previous 3 months. All subjects gave written informed consent. The initial study concluded that neither coenzyme Q_{10} nor remacemide produced significant slowing in functional decline in early HD.

At each visit, participants were evaluated using the Unified Huntington's Disease Rating Scale (UHDRS), a standardized instrument assessing the clinical features and course of HD.[9] This instrument consists of functional, motor, cognitive, and behavioral components. Functional measures included the TFC, Functional Assessment, and Independence Scale. Measures of motor function included the total motor score, maximal dystonia score, and maximal chorea score. Cognitive measures included the Stroop Interference Test, Symbol Digit Modalities Test, and Verbal Fluency Test. Behavior was assessed by frequency and severity of various behaviors, including anxiety, obsessions, and delusions. Supplemental neuropsychological tests included the Brief Test of Attention, Conditional Associative Learning Test (CALT), Hopkins Verbal Learning Test, Trail Making Tests A and B, as well as the Hamilton Depression Inventory.[10–14] Blood samples collected during the study were used for routine safety laboratory assessments by a centralized laboratory. Serum UA levels were obtained from these blood samples at baseline and at months 1, 8, 20, and 30. CAG repeat length was determined for subjects who had never been tested; known repeat length was used for those previously tested.

Baseline UA levels were categorized into quintiles to minimize the influence of any extreme observations on the results. The outcomes were change in scores from baseline to 30 months for each UHDRS measure and supplemental test. Change in TFC score was considered the primary outcome measure as it has been shown to provide a reliable, valid measure of early HD progression and is commonly used as the primary outcome measure in HD clinical trials.[8,9,15] The TFC specifically assesses capacity to work, handle finances, perform domestic chores, and carry out activities of daily living, and required care level. Analysis of covariance was used to assess the association between baseline UA quintile and the change in score from baseline to 30 months for each outcome with gender, study site, baseline age, CAG repeat length, and baseline value of the outcome as covariates.[16] Models that further

adjusted for treatment assignment did not appreciably alter the results and are not presented here. Tests for linear trend among the UA quintiles were performed by testing significance of a linear contrast among the adjusted group means in the analysis of covariance models. Since men generally have higher UA levels than women, an interaction term for gender and UA was assessed in additional analyses to determine if the association between UA and functional decline was different for men and women. Regression-based multiple imputation was used to account for missing data for the 38 subjects who withdrew prior to the 30 month visit. The imputation model included treatment assignment, study site, and values of the outcome variable at all prior visits. The multiple imputation approach appropriately accounts for the uncertainty associated with the imputed values in the computation of standard errors and p-values.17

Results

Subjects ranged in age from 18–75 years (mean 47.9 years); 51% were male. Baseline UA levels ranged from 1.9–9.6 mg/dL (mean 4.5 mg/dl). The average baseline TFC, CAG repeat length, age, and years of education of the subjects were similar across the UA quintiles. Subjects in the highest UA quintile had lower mean total motor scores at baseline than subjects in the first and third quintiles. Caucasians comprised the majority of the sample and were distributed comparably among the five groups. As expected, men had higher baseline UA levels than women (Table 1).

An independent association controlling for gender, study site, baseline age, CAG repeat length, and baseline TFC score was found between baseline UA quintile and the primary outcome, change in TFC over 30 months (adjusted mean worsening in TFC scores: 3.17, 2.99, 2.95, 2.28, 2.21 from lowest to highest quintile, $p=0.03$ for linear trend, partial $R^2=0.034$). A tendency toward less worsening in total motor scores was also found with increasing UA levels (adjusted mean worsening in scores: 14.27, 13.02, 11.56, 12.15, 9.70 from lowest to highest quintile, $p=0.07$ for linear trend, partial $R^2=0.030$). No other secondary outcomes based on cognitive, behavioral, neuropsychological, or depression measures were significantly associated with UA quintile (Table 2). There was no evidence for any of the outcome variables that the association between baseline UA quintile and outcome depended on gender ($p>0.05$ for all interaction terms).

Discussion

This study demonstrated an association between higher baseline UA levels and slower HD progression, particularly as measured by TFC. There was also a modest trend toward less worsening in total motor scores with increasing UA levels. This relationship was not demonstrated with cognitive, behavioral, or neuropsychological outcomes. Further study is needed to confirm these associations as well as to examine possible relationships between UA levels and biologic markers of HD progression when valid and reliable markers are identified.

Despite the discovery that HD is a genetic disorder, the etiology of neuronal death in HD as a result of this genetic mutation is unclear. Oxidative damage and metabolic dysfunction have been suggested to have a role in the pathogenesis of HD. The protein product of the genetic mutation in HD, huntingtin, has been suggested to interact with mitochondria, resulting in impaired mitochondrial function.18 Reactive oxygen species production appears to be increased in damaged mitochondria.2 UA is known to be an effective scavenger of reactive oxygen species and has the ability to bind iron, an inducer of oxidative stress.3 The antioxidant properties of UA support the possibility of a protective effect of UA levels on progressive neurodegeneration in HD.

The initial CARE-HD study concluded that coenzyme Q_{10}, another potentially important antioxidant in the study of HD, did not result in significant slowing in functional decline in early HD when given over a 30 month period. There were observed trends of a small benefit with 600 mg/day of coenzyme Q_{10}; however, a treatment recommendation was not warranted.8 The relationship UA, coenzyme Q_{10}, and other antioxidants may have with HD progression is unclear and future studies targeting plausible biological mechanisms as seen with UA may help clarify this association.

Limitations of this study include not being able to control for possible confounders that were not assessed in this study. Also, the CARE-HD study was limited to subjects with early HD. It is unclear how disease severity may affect the results and how representative these findings are in a broader HD population. Strengths of this study include the longitudinal design, the rigorous collection of clinical assessments in a controlled trial, the use of a central laboratory, and the relatively large sample size of subjects with HD.

UA may have therapeutic implications for slowing the progression of HD. Clinical trials assessing dietary or pharmacologic changes in UA levels may be warranted to confirm and expand on these findings. The observed slowing of HD progression with higher UA levels emphasizes the importance of improving the understanding of this relationship as well as the role of UA as a potential predictor and modifiable factor affecting the rate of HD progression.

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Table 1

Subject Characteristics at Baseline by Baseline Uric Acid Quintile

	Uric Acid Quintile				
	1st	2nd	3rd	4th	5th
Sample Size	66	63	72	76	70
Uric Acid (mg/dL), range	1.8–3.3	3.4–4.0	4.1–4.6	4.7–5.5	5.6–9.6
Total Functional Capacity, mean (SD)	9.9 (1.6)	9.8 (1.9)	10.4 (1.8)	10.1 (1.9)	10.6 (1.8)
Total Motor Score, mean (SD)	33.5 (14.2)	32.8 (14.2)	33.2 (14.3)	29.4 (14.4)	26.8 (12.5)
CAG Repeat Length, mean (SD)	45.4 (3.8)	46.0 (4.5)	45.2 (4.8)	44.2 (2.9)	44.5 (4.2)
Age (y), mean (SD)	46.4 (9.7)	47.0 (11.0)	47.3 (11.2)	49.6 (9.0)	49.1 (11.3)
Education (y), mean (SD)	13.2 (2.0)	14.2 (2.5)	14.0 (3.0)	14.6 (2.8)	14.4 (3.3)
Caucasian, %	95.5	93.7	95.8	94.7	95.7
Male Gender, %	6.1	19.1	61.1	72.4	87.1

SD = standard deviation

Table 2

Adjusted Mean Change in Assessments over 30 Months by Baseline Uric Acid Quintile

	Uric Acid Quintile							
	1st	2nd	3rd	4th	5th	p-value for linear trend	Full Model R^2	Uric Acid Partial R^2
Primary Outcome								
Total Functional Capacity	−3.17 (0.34)	−2.99 (0.34)	−2.95 (0.29)	−2.28 (0.29)	−2.21 (0.31)	0.03	0.110	0.034
Secondary Outcomes								
Other Functional Assessments								
Total Functional Assessment	−4.28 (0.59)	−4.81 (0.56)	−4.14 (0.50)	−3.11 (0.51)	−3.53 (0.53)	0.12	0.224	0.015
Independence Scale	−11.31 (1.51)	−12.19 (1.46)	−12.64 (1.26)	−9.48 (1.27)	−10.25 (1.38)	0.37	0.188	0.010
Motor Assessments								
Total Motor Score	14.27 (1.57)	13.02 (1.52)	11.56 (1.34)	12.15 (1.36)	9.70 (1.43)	0.07	0.249	0.030
Maximal Dystonia	2.69 (0.45)	2.26 (0.43)	2.15 (0.38)	2.74 (0.38)	1.75 (0.40)	0.37	0.321	0.023
Maximal Chorea	3.15 (0.69)	2.10 (0.67)	2.50 (0.57)	2.45 (0.58)	1.72 (0.63)	0.30	0.230	0.014
Cognitive Assessments								
Stroop Color Naming	−6.86 (1.47)	−6.78 (1.46)	−5.86 (1.27)	−4.90 (1.29)	−4.34 (1.35)	0.18	0.146	0.012
Stroop Interference Test	−4.86 (1.07)	−4.40 (1.09)	−3.51 (0.93)	−3.15 (0.89)	−2.37 (0.98)	0.10	0.144	0.019
Stroop Word Reading	−12.03 (1.73)	−11.77 (1.68)	−9.71 (1.51)	−9.86 (1.50)	−7.94 (1.60)	0.10	0.170	0.023
Symbol Digit Modalities Test	−4.20 (0.89)	−3.20 (0.81)	−2.08 (0.74)	−3.68 (0.73)	−3.50 (0.78)	0.76	0.105	0.008
Verbal Fluency Test	−4.86 (0.95)	−5.21 (0.97)	−5.86 (0.79)	−6.06 (0.78)	−4.59 (0.86)	0.93	0.243	0.012
Behavioral Assessments								
Behavioral Frequency Total	1.44 (0.64)	0.70 (0.61)	0.49 (0.54)	0.74 (0.53)	0.38 (0.58)	0.36	0.347	0.006
Behavioral Frequency × Severity Total	3.65 (1.93)	3.41 (1.85)	2.50 (1.59)	2.82 (1.60)	1.07 (1.70)	0.39	0.366	0.010
Neuropsychological Tests								
Brief Test of Attention	−1.28 (0.54)	−1.10 (0.49)	−0.78 (0.40)	−1.60 (0.40)	−1.01 (0.43)	0.99	0.235	0.006
CALT Trials to Criterion	−0.63 (2.38)	−3.82 (2.55)	−4.79 (2.09)	0.66 (2.02)	−3.97 (2.12)	0.80	0.491	0.015
CALT Number of Errors	2.30 (3.81)	2.09 (4.00)	1.26 (3.27)	7.28 (3.31)	0.92 (3.14)	0.85	0.384	0.012

	Uric Acid Quintile							
	1st	2nd	3rd	4th	5th	p-value for linear trend	Full Model R^2	Uric Acid Partial R^2
Hopkins Verbal Learning Test	−5.99 (1.15)	−4.54 (1.15)	−4.72 (0.90)	−3.79 (0.92)	−4.40 (0.99)	0.31	0.251	0.006
Trail Making A (log transformed)	0.57 (0.07)	0.59 (0.07)	0.43 (0.06)	0.51 (0.05)	0.45 (0.06)	0.16	0.205	0.021
Trail Making B (log transformed)	0.28 (0.05)	0.28 (0.06)	0.23 (0.04)	0.31 (0.04)	0.23 (0.05)	0.69	0.369	0.012
Hamilton Depression Inventory	0.47 (0.62)	1.16 (0.62)	−0.69 (0.55)	−0.86 (0.53)	−0.06 (0.60)	0.15	0.400	0.015

CALT = Conditional Associative Learning Test

Values are adjusted mean change in outcome (standard error) obtained from an analysis of covariance model that included baseline uric acid quintile (categorical), gender, study site, baseline age, CAG repeat length, and the baseline value of the outcome variable.

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