Plasma Urate and Progression of Mild Cognitive Impairment

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Key Words

Alzheimer's disease • Mild cognitive impairment • Urate • Oxidative stress • Biomarkers

Abstract

Background: Impaired antioxidant defenses are implicated in neurodegenerative disease. The plasma levels of urate, a water-soluble antioxidant, are reduced in Alzheimer's disease (AD). **Objective:** We aimed to test the hypotheses that high plasma urate at baseline is associated with: (1) a reduced rate of conversion from mild cognitive impairment (MCI) to AD and (2) a lower rate of cognitive decline in MCI. **Methods:** Plasma urate was obtained at baseline from 747 participants in a 3-year, randomized, double-blind, placebo-controlled study of donepezil, vitamin E or placebo for delaying the progression of MCI to AD. The association between baseline urate and conversion from MCI to AD was examined by Cox proportional hazards regression. The relationship between baseline urate and cognitive change on the cognitive subscale of the Alzheimer's Disease Assessment Scale was evaluated by longitudinal analysis. **Results:** Baseline plasma urate was not associated with the rate of conversion of MCI to AD. In the placebo arm, high plasma urate was related to a slower rate of cognitive decline over 3 years, although this was not reproduced in the other treat-

ment arms. **Conclusion:** While plasma urate levels did not predict the progression of MCI to AD, high urate may be associated with a reduced rate of cognitive decline in MCI patients not treated with donepezil or vitamin E. The results support the investigation of biomarkers of antioxidant status as risk factors for cognitive decline in MCI.

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Background

The incidence and prevalence of dementia increase markedly with aging. In East Boston, the prevalence of Alzheimer disease (AD) was 3% in 65- to 74-year-olds, 19% in 75- to 84-year-olds and 47% in those over the age of 85 [1]. AD and other forms of dementia are preceded by mild cognitive impairment (MCI), a clinical syndrome of deficient recent memory with minimal limitation of activities of daily living [2]. Treatments to improve cognition or delay progression in dementia and MCI such as cholinesterase inhibitors and vitamin E are only modestly effective [3]. The identification and treatment of

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modifiable risk factors for cognitive decline can reduce the burden of MCI and dementia to patients, families and society.

Oxidative stress and impaired antioxidant defenses may contribute to nerve injury in neurodegenerative disease, and markers of oxidative stress are elevated in AD and MCI [4, 5]. Urate is a water-soluble antioxidant molecule found to be reduced in plasma in AD [6–8]. High urate was associated with a reduced risk of incident Parkinson's disease (PD) in the Health Professionals Follow-Up Study [9], Honolulu Heart Program [10] and Rotterdam Study [11]. High urate in men was also related to a lower rate of PD progression in the PRECEPT clinical trial (Parkinson Research Examination of CEP1348 Trial) conducted by the Parkinson Study Group [12].

The Mild Cognitive Impairment Study was a 3-year, randomized, double-blind, placebo-controlled investigation of donepezil, vitamin E or placebo in delaying the progression of MCI to AD [13]. The standardized diagnostic criteria, recruitment and the long period of careful follow-up allowed assessment of the potential long-term cognitive consequences of elevated urate with detailed information about potential confounders. We tested the hypotheses that high plasma urate at baseline is associated with: (1) a reduced risk of progression of MCI to AD and (2) a lower rate of cognitive decline in MCI.

Methods

Subjects

The Mild Cognitive Impairment Study has been reported in detail [14]. Briefly, 769 subjects with MCI were enrolled from 69 Alzheimer Disease Cooperative Study sites in the USA and Canada. Potential subjects had screening visits from February, 1999, to December, 2000. Patients were randomized to multivitamin with placebo, vitamin E 2,000 IU p.o. q.d. or donepezil 5–10 mg p.o. q.d. The study was conducted over 3 years with clinical evaluations every 3 months for the first 6 months and then every 6 months up to 3 years or until conversion to AD. Subjects who converted during the 36-month trial stopped using the study medication and were given the option of taking open-label donepezil.

Exposure

The exposure measure was plasma urate levels from the baseline labs (SmithKline Beecham Clinical Laboratories). Of the enrolled participants, 22 did not have urate levels at baseline and were excluded from the analysis, reducing the sample size to 747. Urate was modeled as a continuous variable, as quintiles and as gender-specific quintiles in the analyses.

Outcome

For the survival analysis, the outcome was the time to conversion to AD. For the analysis of cognitive change, it was the cogni-

tive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) [15] performed at each study visit. The ADAS-cog evaluates domains of memory, orientation, language and praxis and is scored from 0 to 70 mistakes.

Confounders

Potential confounders were selected based on literature association with either urate levels or AD risk: age, sex, body mass index, presence of the apolipoprotein E $\epsilon 4$ allele, current smoking, history of alcohol use, history of cardiovascular disease, hypertension, and use of nonsteroidal anti-inflammatory drugs and thiazide diuretics.

Analysis

The analysis was exploratory, first in the entire study cohort, followed by stratification by sex (to determine if there was a subgroup effect as in PD), and then in the placebo group only (to control for informative dropouts that occurred in the donepezil arm and in case there was effect modification by treatment).

Cox proportional hazards regression assessed the effect of baseline urate levels on the time to progression to AD adjusted for the potential confounders. Individuals were censored at dropout, death or the end of the study.

The relationship between urate level and mean ADAS-cog scores across time was analyzed using a mixed effects regression model, taking into account the correlation between repeated outcome measures within the same individual. A random coefficient model with a random intercept and random slope was considered. Urate (either as a continuous variable or as quintiles) and confounders were incorporated as fixed terms. The interaction term of urate with time was tested to determine whether urate influenced the trajectory of ADAS-cog scores over time. All analyses were run in R 2.1.1 (www.R-project.org).

Results

Study Population

The distribution of baseline characteristics by quintile of urate is shown in table 1 and is typical of the general population. Males had higher urate levels than females. Individuals with more elevated values of urate were taller, heavier and had a greater body mass index (reflecting the larger proportion of males in the higher quintiles of urate). Higher levels of urate were also associated with cardiovascular disease, hypertension and thiazide use. The baseline cognitive status and number of apolipoprotein E $\epsilon 4$ alleles did not differ among quintiles of urate. The urate quintiles were similarly distributed among the randomization groups.

Survival Analysis

Of the 747 subjects enrolled with baseline urate data, 204 developed possible or probable AD. Kaplan-Meier plots of conversion to AD by quintile of urate overall and

Table 1. Baseline characteristics within each urate quintile

Baseline characteristic	Urate quintile					p value
	Q1 (≤ 3.6 mg/dl)	Q2 (3.6–4.3 mg/dl)	Q3 (4.3–4.9 mg/dl)	Q4 (4.9–5.7 mg/dl)	Q5 (> 5.7 mg/dl)	
Demographics						
Cases	151	149	148	156	143	
Sex						<0.001
Male	39 (26)	59 (40)	88 (59)	114 (73)	109 (76)	
Female	112 (74)	90 (60)	60 (41)	42 (27)	34 (24)	
Age, years	73.21 $\pm$ 6.5	72.2 $\pm$ 7.3	73.3 $\pm$ 7.9	73.1 $\pm$ 6.6	72.3 $\pm$ 8	0.84
History of smoking	57 (38)	53 (36)	66 (45)	66 (42)	65 (45)	0.34
History of alcohol abuse	4 (3)	6 (4)	5 (3)	6 (4)	6 (4)	0.96
Clinical						
Height, cm	163.7 $\pm$ 9.6	166.9 $\pm$ 9.4	168 $\pm$ 10.2	170.4 $\pm$ 9.5	171.1 $\pm$ 10.1	<0.001
Weight, kg	65.1 $\pm$ 12.7	71.8 $\pm$ 13.1	74.3 $\pm$ 12.7	78.3 $\pm$ 13.7	82.2 $\pm$ 15.4	<0.001
BMI	24.2 $\pm$ 4.1	25.7 $\pm$ 4	26.3 $\pm$ 3.8	27 $\pm$ 4.3	28 $\pm$ 4.5	<0.001
Comorbidities						
Cardiovascular	70 (46)	66 (44)	82 (55)	98 (63)	93 (65)	<0.001
Hypertension	47 (31)	34 (23)	44 (30)	67 (43)	66 (46)	<0.001
Medications						
NSAIDs	104 (69)	105 (70)	114 (77)	116 (74)	103 (72)	0.54
Thiazides	19 (13)	13 (9)	14 (9)	24 (15)	36 (25)	0.001
Randomization group						0.15
Placebo	54 (22)	60 (24)	48 (19)	37 (15)	50 (20)	
Vitamin E	46 (18)	47 (19)	49 (19)	65 (26)	45 (18)	
Donepezil	51 (21)	42 (17)	51 (21)	54 (22)	48 (20)	
Genetic – APOE $\epsilon 4$ alleles						0.32
0 $\epsilon 4$ alleles	61 (40)	61 (41)	71 (48)	68 (44)	72 (50)	
1 $\epsilon 4$ alleles	72 (48)	76 (51)	63 (43)	74 (47)	53 (37)	
2 $\epsilon 4$ alleles	18 (12)	12 (8)	14 (9)	14 (9)	18 (13)	
Cognitive						
MMSE	27.2 $\pm$ 1.8	27.5 $\pm$ 1.8	27.2 $\pm$ 1.9	27.3 $\pm$ 1.8	27.2 $\pm$ 1.9	0.47
ADAS-cog	11.7 $\pm$ 4.7	10.9 $\pm$ 4.5	11.3 $\pm$ 4.1	11 $\pm$ 4.2	11.3 $\pm$ 4.4	0.65

Figures are means $\pm$ SD or numbers of cases with percentages in parentheses. p value for difference in medians (Kruskal-Wallis test) or proportions (Fisher's exact test) among the quintiles. Q = Quintile; BMI = body mass index; NSAIDs = nonsteroidal anti-inflammatory drugs; APOE = apolipoprotein E gene; MMSE = Mini-Mental Status Exam.

by treatment arm are shown in figure 1. Although not significant, the rate of conversion to AD was higher in the lowest quintile of urate in the placebo arm. Urate level (either continuous or by quintiles) was not associated with progression to AD in the entire cohort, within treatment arms or within gender groups.

Longitudinal Analysis

Plots of mean ADAS-cog over time overall and in each treatment arm are shown in figure 2. Urate did not influence the trajectory of decline in the pooled, donepezil or vitamin E analysis. Within the placebo group, the interaction term of urate (continuous) $\times$ time was significant

($p = 0.008$). With urate modeled as quintiles, only the interaction term of the highest quintile with time was significant relative to the lowest quintile ($p = 0.005$). The rate of decline in the highest quintile was 1.49 points per year slower than the lowest quintile.

Discussion

High levels of urate have been associated with diabetes, hypertension and ischemic white matter lesions [16], which are risk factors for cognitive impairment. Based on the antioxidant properties of urate and the association of

Fig. 1. Kaplan-Meier curves for conversion from MCI to AD for each quintile of urate (milligrams/deciliter) overall (**a**) and within the placebo (**b**), vitamin E (**c**) and donepezil (**d**) arms.

lower urate levels with more rapid progression of PD, we hypothesized, instead, that high levels of urate would decrease the risk of AD and cognitive decline in this prospective study of 747 individuals with MCI participating in a clinical trial. The analyses in this report did not reveal a relationship of plasma urate levels with progression of MCI to a clinical diagnosis of AD in the overall sample

and also for males and females separately. Although we did not find consistent evidence across treatment arms of an effect of urate on cognitive decline by ADAS-cog, within the placebo arm there was a significant association between low plasma urate and faster cognitive decline.

Many but not all prior studies reported lower urate levels in AD and MCI patients [7, 17–19]. On the other

Fig. 2. Mean ADAS-cog score by month for each quintile of urate (milligram/deciliter) overall (**a**) and within the placebo (**b**), vitamin E (**c**) and donepezil (**d**) arms.

hand, in a recent trial of 96 community-dwelling elderly, those with high normal levels of urate performed in the lowest quartile of cognitive testing for working memory and verbal learning/memory [20]. In the current study, we found no association of quintile of urate with cognitive status at baseline among the MCI individuals.

The results should be interpreted in the context of potential limitations. MCI is not a homogeneous disease process, and this heterogeneity may have diluted a urate association in a subset of study subjects. While up to 6–25% of MCI individuals per year progress to AD, MCI can reflect other processes impairing cognition [2]. It is possible that the treatments (vitamin E, donepezil) and treat-

ment-related dropouts confounded the association between urate and cognitive decline or incident AD that was suggested by the longitudinal ADAS-cog analysis in the placebo group. The exposure measure is urate from plasma drawn at screening. A single urate level does not necessarily reflect long-term cumulative values, and the relevant risk window for effects of urate on the development of AD may precede the MCI diagnosis. The intra-class correlation coefficients for the 2–4 urate measurements performed at least 1 year apart per subject in this study ranged from 0.71 (vitamin E arm) to 0.80 (placebo arm), suggesting that the single baseline urate measurement can reliably categorize average urate levels over a 3-year period in these MCI subjects. Finally, while urate levels and vitamin E treatment were not associated with risk of AD in this clinical trial, other antioxidant thera-

pies and plasma markers of antioxidant status remain to be similarly studied.

In conclusion, urate levels at baseline did not predict the development of AD in this clinical trial sample. The association of urate with disease risk and progression appears greater in PD. However, the link between low urate and faster cognitive decline in the MCI patients not taking vitamin E or donepezil is suggestive and merits follow-up in additional studies.

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