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Serum Uric Acid and Cognitive Function in Community-Dwelling Older Adults

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Among possible markers of age-related cognitive decline, uric acid (UA) is controversial because it has antioxidant properties but is increased in diseases that often lead to cognitive impairment. In this study of 96 elderly adults, participants with mildly elevated (but normal) serum UA were 2.7 to 5.9 times more likely to score in the lowest quartile of the sample on measures of processing speed, verbal memory, and working memory. Even after controlling for age, sex, race, education, diabetes, hypertension, smoking, and alcohol abuse, the multivariate-adjusted odds of poor verbal memory and working memory remained significant ($ps < .05$). Despite its antioxidant properties, these findings suggest that even mild elevations of UA might increase the risk of cognitive decline among older adults.

Keywords: cognitive aging, biomarker, uric acid, cardiovascular disease, mild cognitive impairment

Theories of cognitive aging often focus on the role of putative biological markers and medical comorbidities to explain age-related cognitive decline. In addition to age and sex, many genetic, nutritional, neuroanatomic, cerebrovascular, and metabolic markers have been shown to alter the risk of cognitive decline or dementia in elderly adults (Flirski & Sobow, 2005; Foster, 2006). Understanding how such factors operate has received greater attention due to the increased emphasis on early diagnosis of dementia (Mortimer, Borenstein, Gosche, & Snowdon, 2005). Only by understanding how these factors modify normal cognitive functioning will it be possible to elucidate their contribution to more severe cognitive impairment and thereby provide clues to the development of effective therapies (Silvestrelli, Lanari, Parnetti, Tomassoni, & Amenta, 2006).

One class of factors that has received increasing attention includes those associated with cardiovascular health. Hypertension, diabetes, and associated conditions alter the risk of cognitive impairment in both healthy individuals (Brady, Spiro, & Gaziano, 2005; Brands, Biessels, de Haan, Kappelle, & Kessels, 2005) and those who are developing or in an early stage of dementia (Newman et al., 2005; Skoog & Gustafson, 2003; Solfrizzi et al., 2004). Because both hypertension and diabetes can cause renal injury (Griffin, 2006; Sarafidis & Ruilope, 2006), kidney function might serve as a biomarker for hypertension-related damage to the central nervous system (Kurella et al., 2005).

The aim of this study is to investigate the relationship between levels of uric acid (UA), a byproduct of purine metabolism (mainly in the kidney), and cognitive functioning in the elderly. This is important because evidence for the effects of UA on normal cognitive functioning is equivocal. Early studies found that serum UA concentration correlated with greater occupational success (Dunn, Brooks, Mausner, Rodnan, & Cobb, 1963) and with higher IQ (Stetten & Hearon, 1959). Uric acid is a natural antioxidant that may have beneficial properties. For example, higher levels of serum UA are associated with reduced risk of Parkinson's disease (de Lau, Koudstaal, Hofman, & Breteler, 2005) and lower concentrations of UA were found in adults with Alzheimer's disease (Rinaldi et al., 2003). Yu, Bruce-Keller, Goodman and Mattson (1998) demonstrated neuroprotective properties of UA in experimental models of stroke. However, early investigators who found that elevated UA correlated with higher achievement did not control for confounding variables, and Ahern, Johnson, and Ashton (1980) found no relationship between IQ and hyperuricemia. Moreover, despite its putative beneficial properties, elevated serum UA predicts the occurrence of stroke (Hozawa et al., 2005) and is associated with worse outcomes following stroke (Mazza et al., 2001; Weir, Muir, Walters, & Lees, 2003) and other cardiovascular events (Short, Johnson, & Tuttle, 2005). In addition, UA usually is elevated in persons with hypertension, atherosclerosis, Type 2 diabetes, and the metabolic syndrome (Hayden & Tyagi, 2004; Sundstrom et al., 2005), all of which increase the risk of cognitive impairment or dementia (Launer, 2005; Newman et al., 2005; Skoog & Gustafson, 2003; Solfrizzi et al., 2004; Yaffe et al., 2004).

Uric acid's seemingly contradictory properties have brought it into focus as a molecule that might contribute to the pathophysiology of diseases with cognitive morbidity, prevent oxidative brain

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injury, or both. In this study, we analyzed the relationship between serum UA and cognitive functioning in a community sample of reasonably healthy elderly adults. We focused on elderly adults because they are at greatest risk of cognitive impairment as a result of vascular, endocrine, and degenerative diseases. We focused on those with serum UA levels in the normal range because finding an association between cognitive functioning and serum UA levels in this range would have significant implications for both public health and treatment. We hypothesized that mildly elevated but normal levels of serum UA would correlate with poorer cognitive test performance.

Method

Participants

Data used for this analysis were drawn from a community sample of 301 adults who were recruited through random digit dialing or written invitation to Medicare beneficiaries age 65 and older to participate in a study of normal aging. Subjects gave written informed consent, and the study was approved by the Johns Hopkins Medicine Institutional Review Board. Each participant underwent a physical and neurological examination, a psychiatric interview, laboratory blood studies, a brain MRI scan, and neuropsychological testing on the same day. We excluded 161 individuals who were younger than 60 years old; 23 who did not complete blood testing; 20 who had a history of stroke, dementia, Parkinson's disease, multiple sclerosis, renal failure, severe traumatic brain injury, or meningioma, or who earned a score of less than 24 out of 30 on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975); and 1 who was receiving antihyperuricemic treatment for gout. This left a final sample of 96 men and women whose demographic characteristics are shown in Table 1.

Procedure

Cognitive measures and serum UA assay. The tests and measures used for this study included Ward's (1990) seven-subtest form of the Wechsler Adult Intelligence Scale—Revised, from which raw scores for the Information, Similarities, Arithmetic, Digit Span, Picture Completion, Block Design, and Digit Symbol subtests were used (Wechsler, 1981), the Hopkins Verbal Learning Test—Revised (Brandt & Benedict, 2001), and the Brief Visuospatial Memory Test—Revised (Benedict, 1997) from which total learning over trials and delayed free recall scores were recorded, the Perceptual Comparison Test from which the total number correct was used (Salthouse, 1991), a test of verbal fluency from which the total number of words beginning with the letters S and P (Letter Word Fluency) and animal names and supermarket items (Category Word Fluency) given in consecutive 1-min trials were recorded, and the Rey Complex Figure Test from which copy accuracy scores were used (Rey, 1941). In order to reduce the number of cognitive variables, each of the 16 specific measures was *z*-transformed and assigned to one of seven cognitive domains, as shown in Table 2. Each participant's domain scores consisted of the sum of his or her *z*-transformed scores on the individual measures that comprised them. The cognitive domains all showed good to excellent internal consistency, with coefficient alphas ranging from 0.61 to 0.92. Finally, serum UA was measured with an Olympus chemistry analyzer (Olympus America, Melville, NY) following the methods described by Fossati, Prencipe, and Berti (1980).

Statistical analyses. Examination of the associations between serum UA and age, body mass (BMI: weight in kilograms divided by the square of height in meters), and years of education was based on Pearson *r* correlations. Associations between serum UA and sex, race, and presence vs. absence of self-reported hypertension, diabetes, current tobacco use, or history of alcohol abuse or dependence were assessed using chi-square analyses. Finally, we conducted unadjusted and multivariate adjusted logistic regressions to determine whether subclinical elevations of serum UA were associated with increased odds of showing below average cognitive test performance. For these analyses, we first identified the highest quartile of serum UA levels for men (≥5.8 mg/dL) and women (≥4.8 mg/dL) in our sample. Participants whose concentrations fell in this quartile were designated as having "high" UA (although it should be emphasized that their values were within normal limits). The remaining participants were classified as having "low-moderate" UA. We next identified participants who scored in the lowest quartile (i.e., below average) of each cognitive domain. By definition, the remaining participants demonstrated at least average performance in the same domain. For the unadjusted analyses, we regressed performance (low vs. average) in each cognitive domain on serum UA (high vs. low-moderate). We then corrected for possible overestimation of odds ratios by entering covariates that are associated with elevated serum UA, poor cognitive test performance, or both. These included age, sex, race, education (years), BMI, and self-reported presence of hypertension, diabetes, current tobacco use, or history of alcohol abuse/dependence. They were entered, with serum UA status, into the model for each cognitive domain with a backward elimination procedure.

Results

Serum UA levels ranged from 1.5 to 7.1 mg/dL for women and 1.5 to 7.6 mg/dL for men. Their corresponding means and standard deviations are shown in Table 1. As expected, serum UA levels correlated significantly with age (Pearson $r = .25$; $p = .013$)

Table 1
Participant Characteristics

Characteristic	Men ($n = 48$)	Women ($n = 48$)	*p*
Age (years)	73.7 ± 7.6	72.4 ± 7.8	.42
Education (years)	14.6 ± 3.3	13.4 ± 3.2	.07
Race (% Black)	10.4	8.3	.73
Mini-Mental State Exam	28.0 ± 1.5	28.3 ± 1.3	.33
Serum UA (mg/dL)	5.0 ± 1.2	4.1 ± 1.4	.001
Weight (kg)	82.7 ± 13.7	70.9 ± 16.1	.001
Body mass index	26.6 ± 3.9	26.7 ± 5.5	.88
Hypertension (%)	40.0	53.2	.21
Diabetes (%)	18.8	10.4	.25
Smokes (%)	21.7	17.0	.57
History alcohol abuse or dependence (%)	14.6	2.1	.03

Note. UA = uric acid. Values presented are as means ± standard deviations unless otherwise indicated.

Table 2
Cognitive Domains, the Measures That Comprise Them, and Their Internal Consistency

Cognitive domain/Tests and measures used	*M* (*SD*)[a]	Coefficient alpha
General verbal		
WAIS–R Information	21.7 (4.7)	.767
WAIS–R Similarities	19.6 (4.6)	
General visuospatial		
WAIS–R Picture Completion	13.6 (3.1)	.798
WAIS–R Block Design	22.7 (8.1)	
Processing speed		
WAIS–R Digit Symbol	40.9 (10.8)	.886
Perceptual Comparison	53.5 (12.6)	
Working memory		
WAIS–R Digit Span forward	6.3 (1.2)	.630
WAIS–R Digit Span backward	4.9 (1.2)	
WAIS–R Arithmetic	11.9 (3.8)	
Verbal memory		
HVLT–R total learning	22.6 (4.8)	.877
HVLT–R delayed recall	7.6 (2.7)	
Visual memory		
BVMT–R total learning	18.0 (6.5)	.923
BVMT–R delayed recall	7.4 (2.6)	
Verbal fluency		
VFT Letter Word Fluency	25.9 (8.8)	.607
VFT Category Word Fluency	39.7 (9.5)	

Note. WAIS–R = Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981); Perceptual Comparison = Salthouse Letter and Pattern Perceptual Comparison (Salthouse, 1981); HVLT–R = Hopkins Verbal Learning Test—Revised (Brandt & Benedict, 2001); BVMT–R = Brief Visuospatial Memory Test—Revised (Benedict, 1997); VFT = Verbal Fluency Test (Schretlen, Munro, Anthony, & Pearlson, 2003).
[a] Data are reported as raw scores.

and body mass ($r = .38$; $p = .0001$). They were higher for men than women (4.96 ± 1.23 vs. 4.09 ± 1.37), $t(94) = 3.27$, $p = .001$, but they did not differ by race, $t(94) = 0.64$; $p = .524$. The 43 participants with hypertension had higher UA levels than those without (4.87 ± 1.27 vs. 4.24 ± 1.39); $t(94) = -2.30$, $p = .024$. The 18 smokers showed a trend toward lower serum UA than nonsmokers (3.99 ± 1.48 vs. 4.64 ± 1.32; $t(94) = 1.84$, $p = .069$. Although the 14 participants with diabetes mellitus had higher levels of UA than those without, this difference was not significant, $t(94) = -1.23$, $p = .222$. Nor were the UA levels of 8 participants who reported any past or current alcohol abuse or dependence significantly higher than those who did not, $t(94) = -0.71$, $p = .481$.

The first series of logistic regressions revealed that, compared to participants with low-moderate levels, older adults with high serum UA were significantly more likely to show below average performance in three cognitive domains. These included processing speed (*OR* = 5.91; 95% *CI* = 2.14–16.29), working memory (*OR* = 3.51; 95% *CI* = 1.30–9.46), and verbal learning/memory (*OR* = 2.71; 95% *CI* = 1.01–7.31). When we corrected for possible overestimation of the odds by adding age, sex, race, years of education, and self-reported hypertension, diabetes, smoking, and history of alcohol abuse or dependence as covariates, high serum UA remained associated with increased risk of below average performance on measures of working memory (*OR* = 4.25; 95% *CI* = 1.44–12.57) and verbal learning/memory (*OR* = 5.02; 95% *CI* = 1.24–20.30). Correcting the processing speed model for these covariates reduced the odds of below average performance associated with "high" serum UA to a nonsignificant level (*OR* = 3.12; 95% *CI* = 0.84–11.61; $p = .09$). The unadjusted and multivariate adjusted odds (and 95% confidence intervals) of scoring in the lowest quartile of each cognitive domain by participants with high serum UA are shown in Table 3.

Discussion

In this study, relatively healthy older men and women with serum UA at the high end of the normal range were significantly more likely than those with low-moderate UA concentrations to perform in the lowest quartile on cognitive testing in three of seven

Table 3
Number (Percentage) of Participants Who Scored in the Lowest Quartile of Each Cognitive Domain and the Corresponding Unadjusted and Multivariate-Adjusted Odds Ratios

	Number (%) in lowest quartile		
Cognitive domain	Low-moderate UA (*n* = 71)	High UA (*n* = 25)	Odds ratio (95% confidence interval)
General verbal	16 (23)	8 (32)	Unadjusted *OR* = 1.62 (0.59 to 4.43) Adjusted *OR* = 1.49 (0.41 to 5.44)
General visuospatial	15 (21)	9 (36)	Unadjusted *OR* = 2.10 (0.78 to 5.68) Adjusted *OR* = 1.00 (0.25 to 3.95)
Processing speed	11 (16)	13 (52)	Unadjusted *OR* = 5.91*** (2.14 to 16.29) Adjusted *OR* = 3.12 (0.84 to 11.61)
Working memory	13 (18)	11 (44)	Unadjusted *OR* = 3.51* (1.30 to 9.46) Adjusted *OR* = 4.25** (1.44 to 12.57)
Verbal memory	14 (20)	10 (40)	Unadjusted *OR* = 2.71* (1.01 to 7.31) Adjusted *OR* = 5.02* (1.24 to 20.30)
Visual memory	18 (25)	4 (16)	Unadjusted *OR* = 0.56 (0.17 to 1.85) Adjusted *OR* = 0.35 (0.10 to 1.26)
Verbal fluency	18 (25)	6 (24)	Unadjusted *OR* = 0.93 (0.32 to 2.69) Adjusted *OR* = 0.45 (0.13 to 1.62)

* $p < .05$. ** $p < .01$. *** $p < .001$.

domains. This association remained even after adjusting for the possible confounding effects of age, sex, race, years of education, hypertension, diabetes, smoking, and past alcohol abuse. These findings suggest that high normal concentrations of serum UA should be added to the growing list of cardiovascular and metabolic biomarkers of mild cognitive impairment among elderly adults.

The mechanism linking UA to cognitive functioning is unknown. Elevated UA commonly accompanies hypertension, hyperlipidemia, obesity, renal disease, insulin resistance, and the metabolic syndrome (Hayden & Tyagi, 2004; Weir et al., 2003). Elevated UA is associated with or increases the risk of cardiovascular disease (Sundstrom et al., 2005), and it increases the likelihood of cardiovascular events in persons with diabetes (Lehto, Niskanen, Ronnemaa, & Laakso, 1998), although its role as a causal factor is controversial (Wannamethee, 1999). Because diabetes and hypertension can lead to cognitive impairment via cerebrovascular disease (Launer, 2005; Skoog & Gustafson, 2003), elevated UA might affect cognitive functioning through cerebrovascular changes. Consistent with this, in comparison with healthy controls, cerebrospinal fluid UA levels were increased in patients with vascular dementia but decreased in patients with Alzheimer's disease (Tohgi, Abe, Takahashi, & Kikuchi, 1993). These investigators argued that elevated UA in persons with vascular dementia was due to damage of the blood–brain barrier.

How can our findings be reconciled with evidence that UA is an antioxidant that might protect against the development of Alzheimer's and Parkinson's disease? One possibility is that, despite being an antioxidant, UA can acquire pro-oxidant properties that damage the vascular endothelium in certain conditions (Patterson, Horsley, & Leake, 2003). It might even play a key role in the development of accelerated atherosclerosis (Hayden & Tyagi, 2004). Using ultrasound to measure flow-mediated dilation, Kato et al. (2005) found that healthy, mildly hyperuricemic men without cardiovascular disease showed impaired endothelial-dependent vasodilation as compared with healthy men without hyperuricemia. Alternatively, animal research has shown that UA impedes the Na+, K+ ATPase modulation of neuronal activity, suggesting the possibility that it might also have direct neurotoxic effects (Bavaresco et al., 2004). Finally, whereas our findings are consistent with the hypothesis that UA affects cognitive function, we cannot exclude the possibility that serum UA increased in response to some other pathological process that caused the cognitive impairment. Yaffe et al. (2004) found an association between the metabolic syndrome and risk of mild cognitive decline in elderly adults, but only among those with high inflammation. Thus, in future studies of UA and cognition, it might be useful to covary inflammation. Alternatively, an analysis that includes measures of cerebrovascular changes could provide stronger (but still indirect) evidence that ischemic changes mediate the relationship between UA and cognition. In any case, the present findings point to a relationship between UA and cognitive functioning that is at least partly independent of most cerebrovascular risk factors.

The associations observed in this study hold for values that span the normal range of serum UA and cognitive test performance. Because these data were based on a broadly representative community sample, the finding that even normal elevations of serum UA are associated with reduced cognitive performance might have broad public health implications. Indeed, these findings might justify a clinical trial to determine whether administration of a xanthine oxidase inhibitor or uricosuric medication would improve the cognitive functioning of elderly adults with elevated uric acid and mild cognitive impairment.

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