Cerebral Ischemia Mediates the Effect of Serum Uric Acid on Cognitive Function

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Background and Purpose—High normal concentrations of serum uric acid (UA) are associated with mild cognitive dysfunction and increased cerebral ischemia as indexed by white matter hyperintensity volumes. We hypothesized that individual differences in white matter hyperintensities mediate the association between UA and mild cognitive dysfunction.

Methods—One hundred eighty community-dwelling adults aged 20 to 96 years completed neuropsychological testing, laboratory blood studies, and a brain MRI scan.

Results—Serum UA was associated \((P<0.05)\) with greater white matter hyperintensities and poorer working memory, processing speed, fluency, and verbal memory. Associations remained after controlling for age, sex, race, education, hypertension, diabetes, alcohol abuse, smoking, and body mass. Adding a term for white matter hyperintensity attenuated these associations such that UA no longer predicted cognitive performance.

Conclusions—Severity of cerebral ischemia might mediate the association between UA and cognitive dysfunction. Even mild elevations in UA appear to contribute to structural and functional brain changes. \((\text{Stroke}.\ 2008;39:3418-3420.)\)

Key Words: brain ischemia ■ neuropsychology ■ uric acid ■ cognitive impairment ■ white matter disease ■ aging

Cerebral white matter hyperintensities (WMH) frequently represent cerebral ischemia and are associated with cerebrovascular risk factors and mild cognitive dysfunction.\(^1\) Although serum uric acid (UA) is an antioxidant and might have neuroprotective properties, elevated UA also accompanies conditions that increase the risk of cognitive dysfunction.\(^2\) We recently found that older adults with high normal concentrations of serum UA are 2.7 to 5.9 times more likely to score in the bottom quartile on measures of processing speed, verbal memory, and working memory.\(^3\) We also found that adults with high normal serum UA levels are 2.8 times more likely to show greater than average WMH burden.\(^4\) We assessed whether cerebral ischemic burden mediates the association between serum UA and mild cognitive dysfunction.

Materials and Methods

Participants
Participants \((n=301)\) were drawn from a community sample of adults recruited for a study of normal aging. Subjects provided written informed consent and the study was approved by the Johns Hopkins Medicine Institutional Review Board. We excluded 121 who did not complete or produce useable MRI or blood laboratory results, were taking antihyperuricemic medication, or did not complete cognitive testing. Table 1 presents demographic characteristics of the final sample \((n=180)\).

Procedure
Participants completed the evaluation on a single day. MRI parameters and WMH assessment methods are described elsewhere.\(^4\) Blinded to participant characteristics and using a region-of-interest approach, all observable WMH were manually traced.\(^4\) WMH volumes were calculated and are expressed as the proportion of WMH to total brain volume. Serum UA was measured from a nonfasting blood sample with an Olympus chemistry analyzer \((\text{Olympus America, Melville, NY})\). Participants completed an extensive neuropsychological test battery yielding 28 cognitive test scores (see supplemental data, available online at http://stroke.ahajournals.org).

Statistical Analysis
Each test score was z-transformed and assigned to one of 8 cognitive domains (see Table 2). Coefficients alpha ranged from 0.76 to 0.93. Pearson correlations explored zero-order relationships among WMH burden, serum UA, and cognition.

To test for mediation, we conducted 2 series of hierarchical multiple regressions using the 4 cognitive factors that correlated with both serum UA and WMH. In both series, we regressed each cognitive domain score on demographic and health variables (age, sex, race, education, hypertension, diabetes, history of alcohol abuse/dependence, tobacco use, and body mass index) en bloc at Step 1. We then added terms for serum UA and total WMH volume...
Table 1. Demographic and Clinical Characteristics

| Table 2. Pearson Correlations Among Cognitive Domains, Serum UA, and WMH Volume  

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| Table 3. Hierarchical Multiple Regression Analyses Demonstrating That WMH Volume Mediates the Association Between Serum UA and Cognitive Functioning |

**Results**

As seen in Table 2, higher serum UA correlated with increased WMH volume and worse performance on tests of working memory, processing speed, fluency, and verbal memory. WMH volume correlated inversely with performance in 7 of 8 cognitive domains.

Table 3 (Model 1) shows that, after adjusting for demographic and health variables (Step 1), higher serum UA concentrations accounted for additional variance in performance on tests of working memory, fluency, and verbal learning/memory. Beta weights for serum UA at Step 2 were −0.20, −0.17, and −0.21 (all P<0.05), respectively, for these 3 models. UA’s association with processing speed failed to reach statistical significance (β=−0.12, P=0.053). Thereafter, adding a term for WMH volume (Step 3) improved the models for working memory, processing speed, and ideational fluency, but not verbal learning/memory, and attenuated the initial beta weights for serum UA to nonsignificant levels (all P>0.05).

Table 2. Pearson Correlations Among Cognitive Domains, Serum UA, and WMH Volume

| Table 3. Hierarchical Multiple Regression Analyses Demonstrating That WMH Volume Mediates the Association Between Serum UA and Cognitive Functioning |

| Model 1  

| Model 2  

In Model 2, after adjusting for demographic and health variables (Step 1), adding a term for WMH volume (Step 2) explained additional variance in test performance in all 4 cognitive domains (βs=−0.17 to −0.25, P<0.05). In these analyses, however, adding a term for serum UA (Step 3) did not improve the statistical models for any cognitive factor. Nor did it significantly reduce the beta weights obtained for WMH at Step 2 for working memory, processing speed, or ideational fluency (βs=−0.18 to −0.23; all P<0.01).

In sum, both higher UA levels and greater WMH burden were associated with worse performance on tests of working memory, processing speed, ideational fluency, and verbal memory even after controlling for health and demographic variables. However, WMH burden appears to mediate the relationships between UA and performance on tests of working memory, processing speed, and ideational fluency, whereas UA does not appear to mediate the relationships between WMH burden and cognitive performance. There is no mediation apparent with respect to verbal learning/memory, UA, and WMH.

**Discussion**

These findings suggest that severity of cerebral ischemia mediates the previously reported association between serum UA and mild cognitive dysfunction. This effect was present even after controlling for health conditions that are known to be associated with both cerebral ischemia and elevated UA. Furthermore, the observed associations were present in relation to performance on tests of working memory, processing speed, and ideational fluency. These processes are particularly sensitive to cerebral ischemic burden both in healthy adults and those with various illnesses.¹

Even mild elevations of serum UA are associated with cerebral ischemia.¹ Impaired vascular tone and endothelial dysfunction likely contribute to the development of some
ischemic changes, because they permit cerebrospinal fluid to cross the blood–brain barrier and allow interstitial water to accumulate, resulting in areas of edema identified as WMH on brain MRI.\(^5\) The association of UA with nitric oxide represents one possible pathway by which mildly elevated UA could contribute to cerebral ischemia. Nitric oxide is a potent vasodilator that mediates vascular tone in the endothelium, fluctuates inversely with UA in healthy adults,\(^6\) and is inhibited by UA in those with cerebrovascular risk factors.\(^7,8\) Decreased endothelial-dependent vasodilation, as assessed by brachial flow-mediated dilation (a noninvasive measure of endothelium-derived nitric oxide activity), is associated with both mild hyperuricemia\(^9\) and increased WMH.\(^10\) These findings support the idea that mechanisms contributing to impaired endothelial functioning and vascular tone play a role in the development of cerebral ischemic burden. It also appears plausible that increased UA could reduce nitric oxide availability in the brain, contributing to endothelial dysfunction and the subsequent development of WMH. However, this potential mechanism is speculative, and many other factors affect cerebrovascular tone and endothelial integrity. There are also other potential means by which UA could contribute to endothelial dysfunction such as through the acquisition of pro-oxidant properties.\(^11\)

Extending these cross-sectional findings with longitudinal studies would be helpful to determine whether elevated UA increases the risk or rate of cognitive decline in elderly adults. A clinical trial may also be useful in determining whether the administration of medications aimed at reducing the production of serum UA would reduce the incidence of ischemic brain disease and associated cognitive dysfunction.

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**References**

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