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LETTER

Pathway for ascertaining the role of uric acid in neurodegenerative diseases

Uric acid is the end product of purine metabolism. Elevated serum urate level, a condition known as hyperuricemia, is a cardiovascular disease risk factor.[1–3] Low urate level, a condition known as hypouricemia, is a risk factor for developing neurodegenerative diseases.[4] The upper normal uric acid levels could range between 6 and 6.8 mg/dL in healthy adults with normal kidney function. Maintaining normal urate levels provides significant antioxidant and neuroprotective effects. High urate levels above saturation threshold (6.8 mg/dL) are considered a pro-inflammatory condition, leading to increased oxidative stress, increased renin–angiotensin levels, activated aldosterone system, increased systemic vascular resistance, and reduced renal blood flow, and consequently hypertension and worsening kidney function.[5] Low serum urate levels are a risk factor for developing neurodegenerative diseases (Figure 1). Although the exact mechanism that uric acid exerts as a neuroprotective biochemical is not elucidated, it is believed that uric acid levels are scavengers of free radicals, superoxide, and hydrogen peroxide.[6] Urate levels are responsible for 55% of free radicals' scavenging capacity in the human body.[6,7] Thus, low uric acid levels could augment the risk of oxidative stress, increasing the accumulation of reactive oxygen species, which may permeate the effect of tau protein on neuro entanglement, leading to a decline in cognitive function and preclinical neurodegenerative diseases.

The study by Fatima et al.[8] provides a mechanism-based approach for the possible role of serum urate in neurodegenerative diseases, in particular, Alzheimer's Disease (AD). As the global aging population grows, the global burden of neurodegenerative diseases becomes a significant unmet public health need. The neuroprotective and antioxidant effects of serum urate are emerging. Therefore, elucidating the possible neuroprotective mechanism could guide a systematic evaluation of the impact of varying serum urate levels on AD. Nonetheless, this study raises more discussion and creates more questions about the double-edged sword effect of urate levels.

The published study has some limitations regarding the possible role of other clinical confounders that could impact urate levels. Therefore, more discussion about these limitations could improve future study design. For example, uric acid is primarily eliminated by the kidney, and hence, adjusting for baseline kidney function (i.e., estimated glomerular filtration rate [eGFR]) could have allowed for a better signal-to-noise ratio, especially in a relatively older population. Beside kidney function, many factors, such as body mass index (BMI), could also lead to varying levels of serum urate between individuals, and hence, adjusting for BMI would have been warranted. Recognizing the differences in urate metabolism between men and women, stratifying the analysis by sex, is statistically and biologically sound. Moreover, adjusting for baseline uric acid confounders, including BMI and eGFR, would have further improved the signal-to-noise ratio of association between urate levels and cerebrospinal fluid biomarkers, while stratifying the results by sex. Additionally, select medications commonly prescribed to treat chronic diseases, highly prevalent among older adults, can significantly modulate the individual's serum urate levels. For example, low-dose aspirin, diuretics, and beta-blockers could increase urate levels. Other prescribed medications, including losartan, fenofibrate, and sodium-glucose co-transporter-2 inhibitors, may lower serum urate levels. Therefore, a general assessment of the patient's medications could help differentiate inherent urate levels compared to secondary urate levels.

Moreover, urate levels are significantly influenced by sequence genetic polymorphisms, primarily single nucleotide polymorphisms (SNPs), within critical uric acid transporters.[9–12] Given the physiological role of uric acid, as a naturally occurring antioxidant, population genetics studies would suggest that more patients with neurodegenerative diseases would be carriers of the risk alleles associated with lower serum urate levels than controls.[13–15] To test this hypothesis, a case-control study was conducted to estimate the genetic risk score of previously reported eight uric acid loci in patients with Parkinson's disease (PD; $n = 1061$) and without PD ($n = 754$). The study concluded that male patients with PD had lower serum urate levels than controls (5.61 mg/dL vs. 6.27 mg/dL, $P = .04$). Also, the study identified that patients with more than a 9 genetic risk score (range 0–16), associated with low serum urate levels, had odds ratios of 1.55 (95% confidence interval [CI], 1.10–2.18) for PD compared to controls with two to seven risk alleles.[16] In a similar study population, however, serum urate levels did not show a significant effect on the development of dementia in patients with PD.[17] A study by Lu et al.[15] evaluated the potential role of gout and the risk of developing AD in the general population using matched cohort design for age, sex, entry time, and BMI from an electronic database representative of the UK general population. The study identified that gout was protective against developing AD. After

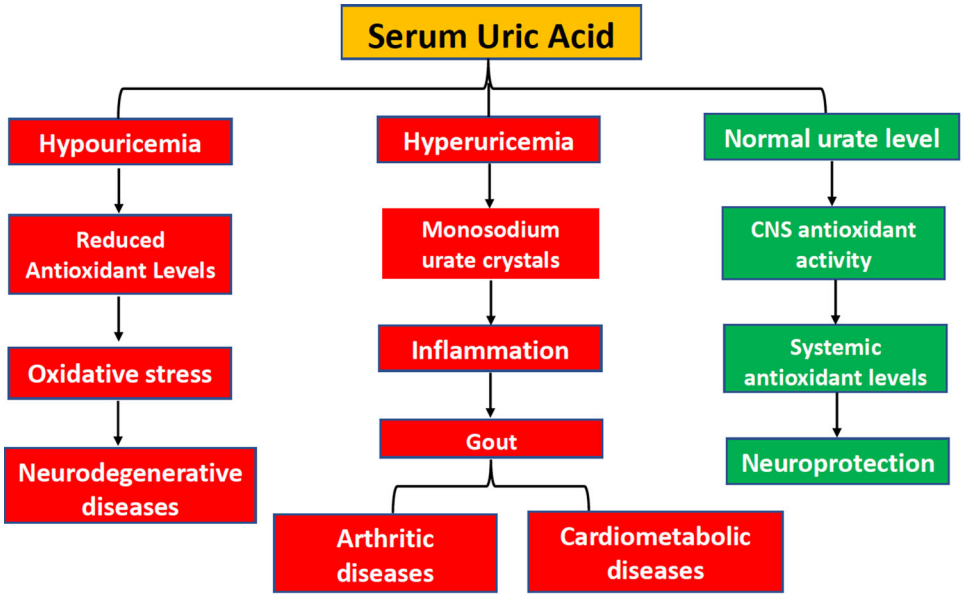

FIGURE 1 The role of serum uric acid levels in human health. CNS, central nervous system

a median follow-up of 5 years, hazard ratios of developing AD among patients with gout were 0.71(95% CI, 0.62–0.80), and 0.76 (95% CI, 0.66–0.87) in univariate and multivariate analyses, respectively.[15]

Finally, the current study by Fatima et al.[8] appears to be consistent with the prior literature.[18,19] However, the employed analysis ushers in a much-needed discussion about research design to characterize the implications of urate production in the brain compared to systemically circulating urate levels as well as the role of the blood–brain barrier in urate transport. Elucidation of these distinct biological processes could be critical in evaluating optimal serum urate levels in neurodegenerative disease prevention or management. Also, quantifying urate levels in cerebrospinal fluid samples is an innovative approach to robustly test the association between the amyloid beta (Aβ), Aβ40 and Aβ42, total tau, phosphorylated tau, and neurofilament light levels and urate levels. This real-time assessment approach would eliminate the effect of plasma uric acid confounders and accurately ascertain the direct or in-dicrect role of the blood–brain barrier in urate transport.

CONFLICT OF INTEREST

The author has nothing to disclose.

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