Role of serum urate in neurocognitive function and dementia: new evidence contradicts old thinking

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In ARD, Latoure et al used the data from a community-based prospective French cohort study of healthy 4931 elderly people 65 years or older, examined at six clinical visits (including cognitive examinations) over 12 years, and analysed 1598 participants with a baseline serum urate level (serum uric acid (sUA)), no diagnosis of dementia, a Mini-Mental State Examination (MMSE) score of ≥24 and at least one follow-up visit.1 Dementia was diagnosed in a 3-step process, screening using the MMSE and the Isacs Set Test by trained psychologists, additional neurological testing by a physician, and adjudication based on criteria by an independent committee of neurologists. Dementia developed in 110 subjects during the 13 357 person years of follow-up. Multivariable-adjusted HR with the highest (≥5.8 mg/dL in men, ≥4.9 mg/dL in women) versus the lowest sUA quartile (≤4.37 and ≤3.51 mg/dL, respectively) was 1.79 for incident dementia (95% CI 1.17 to 2.73; p=0.007). A strong association was seen with vascular or mixed dementia (HR=3.66 (95% CI 1.18 to 10.41), p=0.015), and no significant association was noted with Alzheimer’s disease (HR=1.55 (95% CI 0.91 to 2.61), p=0.10). Several important aspects of this study need to be carefully considered while interpreting findings: (1) patients on urate-lowering therapies (ULTs) were excluded; (2) there was no significant association between sUA levels and MRI markers of cerebrovascular disease or hippocampal volume; and (3) the association between sUA and vascular or mixed dementia was no longer significant, when adjusted for interim strokes. The authors carefully noted that these findings were not generalisable to hyperuricaemia or gout cohorts or to those younger than 65 years.

When one examines other studies in this area, the evidence is contradictory. Some studies showed that hyperuricaemia was associated with a lower risk of dementia,2-4 while other studies showed an opposite effect.5-10 A major limitation is that most of these studies provided the evidence were cross-sectional. Two recently published systematic reviews carefully examined these data and provide a more comprehensive synthesis of the evidence. The first systematic review assessed whether sUA was associated with cognitive impairment and dementia.11 Across 31 studies, using mostly case–control data, sUA was lower in cases of dementia compared with non-dementia controls with a standardised mean difference (SMD) of −0.33 (95% CI not provided; p<0.001).11 In contrast, adjusted logistic regression analysis across five studies suggested no association with increasing sUA (per mg/dL increase) with dementia, with an OR of 1.18 (95% CI 0.96 to 1.46, p=0.12).11 There was no correlation between the sUA level and the scores on MMSE (r=−0.08, p=0.27), except in patients with Parkinson’s disease-related dementia (r=0.155, p=0.003).11 Major limitations were clinical heterogeneity between studies, the risk of bias in studies including publication bias and a small sample size, and a cross-sectional design for most studies.11 The systematic review concluded that the relationship between sUA and dementia/cognitive impairment was not consistent across all dementia groups. Another systematic review assessed the association of sUA with Alzheimer’s dementia.12 Based on 11 case–control studies including 2 708 participants, the sUA levels were not significantly different between patients with Alzheimer’s dementia and healthy controls, and the standardized mean difference (SMD; same as the effect size) for sUA was −0.50 (95% CI −1.23 to 0.22), not statistically significant.12 Therefore, based on these systematic reviews, there is no convincing evidence to date that higher sUA levels are associated with a lower risk of dementia, except possibly in Parkinson’s disease-related dementia.

The current cohort study draws our attention to the association of the sUA level (hyperuricaemia) with the risk of dementia in the elderly using a population-based sample of the French elderly.1 The current study reported an association opposite to what has been a past concern, by showing a significant association of the highest baseline sUA quartile with a 1.8-times higher risk of dementia with up to 12-year follow-up. The study showed that the association of higher sUA level was stronger with vascular or mixed dementia compared with Alzheimer’s disease, hinting at different pathogenic mechanisms for these types of dementia as it relates to sUA levels.1 The lack of association of sUA levels and MRI markers of cerebrovascular disease is an equally interesting negative finding. This negative finding might be related to a small number of incident cases despite a large cohort sample size and/or low sensitivity of this MRI marker for early/incident dementia. In general, a key challenge to any study of dementia or associated risk factors is its long asymptomatic period and a gradual onset in most cases. These challenges can be addressed by the development of more accurate biomarkers of early dementia, an active area of research that holds promise for the future.13-15 Thus, this study adds significantly to the current knowledge base that contains few prospective cohort studies.

This study1 like any well-done study, raises several important questions that future studies should attempt to address: (1) What impact would a change in sUA over time have on the risk of dementia in the elderly? (2) Would the effect be similar in somewhat younger patient populations, that is, those younger than 65 years? (3) Do these risks vary by the presence of cardiovascular or cerebrovascular disease? These are a few questions that this study raises, which can guide the planning of well-designed studies investigating these relationships in the future.

ARE THERE IMPLICATIONS FOR HYPERURICAEMIA AND DEMENTIA RISK IN PATIENTS WITH GOUT? A recent treatment guideline extrapolated the concern related to low sUA and the risk of dementia to the treatment for gout,16 despite a relative lack.

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The current study challenged the view that high sUA is protective against the risk of dementia and showed that high sUA was a risk factor for dementia in the elderly general population. More high-quality longitudinal studies like this study assessing the association between sUA and dementia (and early biomarkers) are needed. There is a need for reproduction of these relationships across various cohorts and an examination of the correlation of sUA level with various imaging and functional assessments for cognition and dementia. New knowledge in this area could open a new line/s of investigation for prevention and treatment of dementia.

**WHAT IS NEXT?**

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