Published Ahead of Print on February 15, 2019 as 10.1212/WNL.0000000000007121

EDITORIAL

Vitamin D

A novel protective factor for delirium?

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Neurology® 2019;92:1-2. doi:10.1212/WNL.0000000000007121

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Delirium is a state of acute brain dysfunction, affecting as many as 50% of older patients in hospital, and is associated with prolonged hospitalization, high health care costs, long-term cognitive decline and dementia, and a substantially increased risk of mortality.[1–3] One postulated mechanism is that delirium results from the breakdown of brain network dynamics triggered by a stressor (e.g., major surgery, general anesthesia, infections, or psychoactive drugs) in individuals with preexisting low brain resilience due to deficits in connectivity or plasticity.[2] Multiple lines of evidence support a strong relationship between delirium and dementia and that these conditions share some pathophysiologic mechanisms, including acetylcholine deficiency, inflammation, and reduced cerebral oxidative metabolism.[3]

Vitamin D is a steroid prohormone with important roles in multiple organs, including the brain. As vitamin D levels are largely determined by the amount of sun exposure on the skin, levels may be lower in individuals with a wide variety of conditions associated with diminished outdoor exposure. Vitamin D receptors are present in brain areas crucial for cognition.[4] Furthermore, evidence indicates that vitamin D has neuroprotective roles and regulates the genetic expression of several neurotransmitters in the brain, such as acetylcholine, dopamine, γ-aminobutyric acid, and serotonin,[4] all of which may be implicated in cognitive disorders, including delirium and Alzheimer disease, a major cause of dementia.[1,4]

A retrospective cohort study of 4,508 patients without a history of dementia showed that deficient levels of prehospital serum 25-hydroxyvitamin D (S-25[OH]D), the clinical marker of vitamin D status, were associated with a greater than 2-fold increased risk of hospital-acquired, new-onset delirium.[5] However, given the observational nature of the study and thus, the possibility of confounding and reverse causality, the causal inference of the association between vitamin D status and delirium is limited. Mendelian randomization studies, which utilize genetic variants as proxy indicators for the risk factor to infer causality, have provided support for a protective association of higher S-25(OH)D levels with risk of Alzheimer disease.[6,7]

In this issue of *Neurology*®, Bowman et al.[8] report the results from the first mendelian randomization study of S-25(OH)D levels in relation to risk of delirium. They used data from 313,121 UK Biobank participants, followed for up to 9.9 years, in whom 544 hospitalized delirium cases were ascertained. Genetically predicted S-25(OH)D levels, across 4 variants in the *GC/DBP*, *NADSYN1/DHCR7*, *CYP2R1*, and *CYP24A1* gene regions, were inversely associated with risk of delirium. The hazard ratio was 0.74 (95% confidence interval 0.62–0.87; p = 0.0004) per 10 nmol/L increase of S-25(OH)D levels. The association remained after exclusion of prevalent cases of dementia and was consistent in other sensitivity analyses. The study further showed that delirium risk was increased in participants with one or more *APOE* ε4 allele (hazard ratio = 3.73; 95% CI 2.68–5.21 for ε4ε4 vs ε3ε3), but showed no interaction between *APOE* and vitamin D–related variants in relation to delirium risk.

Important strengths of the study by Bowman et al.[8] include the large sample size and the mendelian randomization design. The use of genetic variants as proxies for the modifiable risk factor (in this case S-25[OH]D levels) in a mendelian randomization analysis reduces bias caused by confounding,

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because genetic variants are randomly allocated at conception and thus unlikely to be associated with other modifiable risk factors. In addition, reverse causality (i.e., the outcome affects the risk factor and not vice versa) cannot explain the association between S-25(OH)D levels and delirium risk because delirium cannot modify genotype. This is particularly important with vitamin D because of its known association with many other disease states that may predispose to delirium. A limitation of this study is that S-25(OH)D levels were not available for the UK Biobank participants and therefore the genetic variants could not be analyzed concurrently with vitamin D levels.

The validity of the results is dependent on whether the assessed genetic variants affect delirium risk solely through their effects on S-25(OH)D levels, and not through any other causal pathway. A limitation from mendelian randomization studies is pleiotropy, where one gene can influence other mechanisms and these may act in the causal pathway. Bowman et al.[8] used up to 6 genetic variants, previously identified as associated with S-25(OH)D levels (at $p < 5.0 \times 10^{-8}$)[9] as proxies for S-25(OH)D levels. The vitamin D–raising variants in the *GC/DBP* and *AMDHD1* genes were most strongly inversely associated with delirium risk. *GC/DBP* encodes vitamin D binding protein (DBP) and is the variant most significantly associated with S-25(OH)D levels. DBP has other roles beyond the transport of vitamin D, such as modulation of immune and inflammatory responses and binding of fatty acids.[10] Moreover, DBP might attenuate the harmful effects of β-amyloid, and increased DBP levels occur in the CSF of patients with Alzheimer disease.[10] *AMDHD1* (amidohydrolase domain containing 1) encodes an enzyme involved in the catabolic pathway of tryptophan, tyrosine, and other amino acids.[9] Tryptophan and tyrosine are precursors to the neurotransmitters serotonin and dopamine, respectively. Thus, the association between the variant in *AMDHD1* and delirium risk might be mediated through alterations in serotonin and dopamine levels in the brain rather than through S-25(OH)D levels. However, a significant association between genetically predicted S-25(OH)D levels and risk of delirium was observed in the analysis that did not include the variant in *AMDHD1*.[8] The other variants associated with S-25(OH)D have no known association with potential risk factors for delirium.

While an association between vitamin D and delirium is plausible and supported by available observational[5] and genetic[8] data, further research is necessary before a firm conclusion can be reached. The study by Bowman et al.[8] supports the rationale for a randomized trial assessing whether vitamin D supplementation may prevent delirium in older individuals. Experimental studies to elucidate the mechanisms underpinning the potential association between vitamin D and risk of delirium are also warranted.

Study funding

No targeted funding.

Disclosure

S.C. Larsson has received research support from the Swedish Brain Foundation, the Swedish Research Council, and the Swedish Research Council for Health, Working Life and Welfare. L. Flicker reports no disclosures. Go to Neurology.org/N for full disclosures.

References

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–922.
2. Shafi MM, Santarnecchi E, Fong TG, et al. Advancing the neurophysiological understanding of delirium. J Am Geriatr Soc 2017;65:1114–1118.
3. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. Lancet Neurol 2015;14:823–832.
4. Annweiler C, Dursun E, Féron F, et al. Vitamin D and cognition in older adults: updated international recommendations. J Intern Med 2015;277:45–57.
5. Quraishi SA, Litonjua AA, Elias KM, et al. Association between pre-hospital vitamin D status and hospital-acquired new-onset delirium. Br J Nutr 2015;113:1753–1760.
6. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS. Modifiable pathways in Alzheimer's disease: mendelian randomisation analysis. BMJ 2017;359:j5375.
7. Larsson SC, Traylor M, Markus HS, Michaelsson K. Serum parathyroid hormone, 25-hydroxyvitamin D, and risk of Alzheimer's disease: a mendelian randomization study. Nutrients 2018;10:E1243.
8. Bowman K, Jones L, Pilling LC, et al. Vitamin D levels and risk of delirium: a mendelian randomization study in the UK Biobank. Neurology 2019;92:XX–XXX.
9. Jiang X, O'Reilly PF, Aschard H, et al. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat Commun 2018;9:260.
10. Speeckaert MM, Speeckaert R, van Geel N, Delanghe JR. Vitamin D binding protein: a multifunctional protein of clinical importance. Adv Clin Chem 2014;63:1–57.

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DOI 10.1212/WNL.0000000000007121