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Vitamin D and cognitive function in older adults

Are we concerned about vitamin D-mentia?

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In 1983, Goodwin et al.[1] published a seminal article in which they evaluated cross-sectional associations between cognitive function test scores and blood levels of micronutrients in noninstitutionalized, healthy older adults (age >60 y). They found that low blood concentrations of vitamin C, vitamin B12, riboflavin, and folate were associated with poor performance on tests of nonverbal abstract thinking or short-term memory. This was the first epidemiologic evaluation of subclinical micronutrient deficiency and its potential to influence cognitive function in otherwise healthy older adults. In the ensuing 25+ years, hundreds of reports have linked micronutrients to both global and domain-specific cognitive functions, as well as risk of dementia and Alzheimer disease.

The current "hot" vitamin receiving attention is vitamin D, and not simply because it is made in the skin upon exposure to sunlight. Well-recognized for its role in preventing rickets in children and osteomalacia in adults, there is increasing evidence that vitamin D influences a variety of pathophysiologic conditions, including age-related cognitive dysfunction and dementia.[2-4] The vitamin D receptor and the vitamin D activating enzyme, 1,α-hydroxylase, are expressed throughout the brain,[2-4] and vitamin D is known to affect the expression of various neurotrophins and calcium binding proteins that are essential for normal brain function.[2-4] Vitamin D also stimulates neurite outgrowth in human neuroblastoma cells and in rodent embryonic hippocampal explants and progenitor cell lines, and increases hippocampal density in rats.[2] Deficiency of vitamin D in rodents increases ventricle size and alters learning and other behavioral parameters.[2] There is also evidence that vitamin D suppresses the expression of inflammatory cytokines, thus potentially connecting vitamin D deficiency to inflammatory and vascular disease mechanisms underlying neurodegeneration.[2] With estimates that the prevalence of vitamin D deficiency in older adults may exceed 50% depending on time of year, living circumstances, dietary intake, and skin color,[5-7] it is reasonable to postulate that vitamin D deficiency can contribute to age-related cognitive decline.

In this issue of *Neurology*®, there are 3 articles on vitamin D and cognitive function. The first, by Annweiler et al.,[8] is a cross-sectional analysis of community-dwelling women (≥75 y) who participated in the EPIdémiologie De l'OStéoporose (EPIDOS) Study conducted in France during the mid-1990s. Global cognitive function was evaluated using Pfeiffer's Short Portable Mental State Questionnaire (SPMSQ).[9] Vitamin D was determined by measurement of 25-hydroxyvitamin D (25OHD), a circulating metabolite that is an accepted indicator of vitamin D status. Seventeen percent of the subjects had vitamin D deficiency, defined as serum 25OHD <10 ng/mL. Subjects with vitamin D deficiency had a lower mean SPMSQ score than those who were not deficient, as well as an odds ratio for cognitive impairment (SPMSQ <8 out of 10 points) of ~2.0 after controlling for relevant confounders. The authors conclude that vitamin D deficiency is associated with cognitive impairment in elderly women and that vitamin D supplements may improve or maintain cognitive function.

The second report, by Buell et al.,[10] is a cross-sectional study of men and women (≥65 y) who participated in the Nutrition and Memory in Elders (NAME) study from 2003 to 2007. Subjects were evaluated for the presence or absence of dementia and cerebrovascular disease, and underwent MRI to assess overall and regional brain volumes, white matter hyperintensity (WMH), and infarcts. Fourteen percent of the study sample had vitamin D deficiency (25OHD <10 ng/mL) and 44% were classified as vitamin D insufficient (10–20 ng/mL). Compared with subjects who had adequate status, subjects with low vitamin D had higher WMH volume and a higher prevalence of large vessel infarcts. In addition, low vitamin D status was associated with odds ratios

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of ~2.0 for all-cause dementia, Alzheimer dementia, and stroke after controlling for relevant confounders. The authors conclude that vitamin D deficiency is associated with increased risk of dementia and cerebrovascular disease and that vitamin D may have vasculoprotective properties.

The third report, by Slinin et al.,[11] is a longitudinal assessment of community-dwelling men (≥65 y) participating in the Osteoporotic Fractures in Men (MrOS) Study. Baseline recruitment occurred from 2000 to 2002 and mean follow-up was 4.6 y. Cognitive function was assessed using the modified Mini-Mental State Examination (3MS), a test of global cognitive function scored on a scale of 0–100 points,[12] and by the Trails B test, a timed test of executive function.[13] Subjects were divided into quartiles based on baseline serum 25OHD concentrations, with the lowest quartile <20 ng/mL. At baseline, the odds ratios for cognitive impairment (defined as 3MS score <80 or Trails B test time >225 seconds) were between 1.6 and 1.8 in the lowest quartile of 25OHD concentrations compared to the highest quartile. However, these odds ratios did not reach statistical significance, and were greatly attenuated after controlling for race/ethnicity and education. For incident cognitive impairment, the OR for a significant decline in 3MS score was 1.5 in the lowest quartile of 25OHD concentration compared with the highest quartile and the trend across the quartiles was significant. Control for confounding by race/ethnicity and education, however, slightly attenuated the trend, enough to lose statistical significance. Change in Trails B test time was not different among the 25OHD quartiles. The authors conclude that there is little evidence for an association between vitamin D status and concurrent or incident cognitive impairment. They suggest that additional studies should be carried out that include women and tests of other cognitive domains.

What should we make of these studies? First, it is evident that the prevalence of vitamin D deficiency is very high among older adults.[2-7] This is likely due to both inadequate dietary intake and limited exposure to sunlight. This in and of itself could warrant expanded screening for vitamin D deficiency and promotion of supplements. Whether vitamin D supplements will maintain cognitive function in older adults remains an open question. For cross-sectional associations between 25OHD concentrations and cognitive dysfunction/dementia, reverse causation cannot be excluded. Cognitively impaired older adults may eat poorly or they may have reduced exposure to sunlight, which could lead to reduced vitamin D status. The lack of longitudinal associations between low vitamin D status and incident cognitive impairment observed by Slinin et al.[11] perhaps supports this contention. However, this study is itself limited by the lack of women included in the study sample, and because the lowest quartile of vitamin D status consisted of all subjects with 25OHD <20 ng/mL. While values less than 20 ng/mL are indicative of inadequate status, outright deficiency is currently defined as <10 ng/mL. Perhaps a reevaluation of the data comparing deficient subjects (<10 ng/mL) to nondeficient subjects (>20 ng/mL) would reveal significant associations.

What are needed now are placebo-controlled intervention studies to determine if vitamin D supplements will protect against age-related cognitive decline. In the meantime, neurologists and geriatricians should be aware of the high prevalence of vitamin D deficiency in their patient populations and the possibility that supplementation could be beneficial. Adequate intakes of vitamin D for ages 51–70 y and >70 y are currently defined as 10 μg/day (400 IU) and 15 μg/day (600 IU), respectively,[14] or enough to maintain a 25(OH)-vitamin D level of ~30 ng/mL or more. These intakes are primarily for maintaining bone health and are evolving standards. The appropriate intake amounts to support brain function in older adults remain to be determined.

DISCLOSURE

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