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SHORT REPORT

Vitamin B6 and vitamin D deficiency co-occurrence in geriatric memory patients

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Abstract

INTRODUCTION: Vitamin B6 and D levels are not assessed routinely in geriatric memory patients. This study examined vitamin levels to determine the potential effects on cognition.

METHODS: A chart review was conducted of 203 consecutive patients over a 12-month period. Levels of vitamins B1, B6, B12, and D were obtained on the day of clinic to identify deficiencies. A mental status exam (Mini Mental State Examination [MMSE]) was also performed.

RESULTS: One hundred sixty-seven patients had one or more vitamin levels obtained on the day of clinical evaluation. Vitamin B6 deficiency was the most common (37.5%), followed by vitamin D deficiency (36.8%). A chi-square test revealed significant co-occurrence of deficiency of vitamins B6 and D ($p < 0.001$). Vitamin B6 and D deficiencies were associated with lower MMSE scores ($p < 0.05$).

DISCUSSION: Vitamin B6 and D deficiencies are common in geriatric patients. The coexistence of these vitamin deficiencies has a significant association with cognitive performance, indicating the clinical importance of monitoring and supplementation.

1 | INTRODUCTION

Alzheimer's disease (AD) has been marked as a global epidemic, with age being the greatest risk factor for developing the neurodegenerative disease.[1] Vitamin B12 (cobalamin) is routinely checked in memory clinic patients and research subjects, but other central nervous system (CNS)–significant vitamins such as B6 (pyridoxine), B1 (thiamine), and D are not. Vitamin B6 and B12 deficiencies are associated with mild cognitive impairment and dementia.[2,3] Pyridoxine alone can enhance quantitative and qualitative memory through a variety of effects.[4] For example, pyridoxine is required for the synthesis of neurotransmitters, and as such is involved in both neuronal excitation and inhibition.[5]

Vitamins B1 and D are not assessed routinely in memory patients even though they have been found to be associated with brain health and cognition. Thiamine (B1) deficiency is associated with cognitive deficits and encephalopathy, possibly due to reduced brain glucose metabolism.[6] Geriatric memory clinic patients are often deficient in vitamin D, and low levels of vitamin D have been reported to be correlated positively with cognitive test results.[7]

The purpose of the present study is to determine the prevalence of deficiencies in vitamins B1, B6, B12, and D in geriatric memory patients and to explore the possibility of co-occurring vitamin deficiencies and the relationship to baseline cognitive function.

2 | METHODS

This retrospective cross-sectional records review included a consecutive series of 203 new patients presenting to the UW Health Hospital and Clinics Memory Assessment Clinic between June 2019 and June 2020. Of these patients, 164 were assessed for levels of vitamins B1, B6, B12, and D (total 25-(OH)D). Only test results obtained at the clinic on the day of the clinic visit were analyzed. Vitamin B1 was assessed from whole blood sample, whereas vitamins B6, B12, and D were tested from a serum sample. Vitamins B1 and B6 were assessed utilizing quantitative high-performance liquid chromatography (HPLC)/liquid chromatography-tandem mass spectrometry. Vitamin D was assessed via HPLC. Vitamin B12 was assessed using chemiluminescent immunoassay. No fasting or other special arrangements were made for testing. Deficiency thresholds were as follows: vitamin B1 <70,[8] vitamin B6 <30,[9] vitamin B12 <300,[10] and vitamin D (25-(OH)D) <30 ng/mL.[11] All data and results were obtained from the patients' medical records. The Mini Mental State Examination (MMSE) was administered on the date of the clinic visit in order establish a baseline cognitive function.[12] This study was reviewed by the University of Wisconsin Human Subjects Institutional Review Board (IRB) and was approved as meeting exempt status due to the de-identified nature of the retrospective record review.

2.1 | Statistical analyses

Along with descriptive statistics, *t*-test of independent samples, chi-square tests of independence, and risk estimates were conducted. Because vitamins B6 and D were the most frequent vitamin deficiencies in the sample, we further explored the relationship between vitamins B6 and D by including only those patients who had both vitamin levels evaluated ($N = 96$). To determine the relative risk of having a deficiency in vitamins B6 and D a Mantel-Haenszel common odds ratio was calculated.

3 | RESULTS

Records from 203 consecutive patients were reviewed; 164 patients had one or more vitamin levels obtained on the day of the clinic visit. Of the sample of 164 participants, 100 were female and 64 were male. The average age was 78 (mean = 77.51, SD = 7.55). The ethnicity of the population was predominantly White (157 (96%) white, 3 (1.8%) African American, 3 (1.8%) Asian, and 1 (0.6%) Hispanic). There were variable rates of vitamin levels tested across the patient sample. The mean and SD for the vitamin levels are as follows: vitamin B1 (mean = 122.33 nmol/L, SD = 36.86), vitamin B6 (mean = 73.34 nmol/L, SD = 84.59), vitamin B12 (mean = 650.16 pg/mL, SD = 439.52), and vitamin D (mean = 35.91 ng/mL, SD = 14.41). In Table 1, the number of patients who were evaluated for a given vitamin deficiency is indicated as well as the number and percent of patients who were found to have a vitamin deficiency. Vitamin B6 deficiency was the most common, found in 37.5% (48 of 128). The second most common deficiency was vitamin D at 36.8% (43 of 117). Finally, the mean MMSE score for the sample was 25.34 (SD = 4.49).

Of those participants with both vitamin B6 and D levels obtained, 27 of 96 (28.1%) had deficiencies in both vitamins B6 and D. In addition,, 12 (12.5%) had a vitamin B6 deficiency only and 14 (14.6%) had a vitamin D deficiency only. A Pearson chi-square test of independence was calculated comparing the frequency of vitamin B6 deficiency with a co-occurring vitamin D deficiency. A significant relationship was found between the two groups: ($\chi^2(1, N = 96) = 18.884$, $p < 0.001$). In addition, individuals had a 7 times higher relative risk for a deficiency

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and conference presentations. Although nutritional problems with folate and vitamin B12 deficiencies have been reported in memory patients, few reports of vitamin D, and no reports of vitamin B6 deficiency in memory patients were found. Furthermore, no significant co-occurrence of vitamin B6 and D deficiencies has been reported in any clinic population, and the finding that both vitamin B6 and D deficiencies had a significant relationship to mental status screening scores is novel.
2. **Interpretation**: Our findings show that vitamin B6 and D deficiencies are common in the memory clinic patients and should be tested routinely , just as vitamin B12 is currently. The significant co-occurrence indicates that if one is deficient, the other may also be deficient. The association with both vitamins B6 and D on cognitive performance indicates that testing for these vitamin deficiencies should be routine in all memory clinic patients.
3. **Future directions**: Our findings warrant the following efforts: (1) identify the incidence and prevalence of deficiencies in vitamins B6 and D in large memory patient samples; (2) examine the biochemical link in these disparate vitamins; (3) compare neurocognitive testing before and after treatment with vitamins B6 and D to clarify the connection between cognition and these vitamin deficiencies.

TABLE 1 Vitamins tested in geriatric memory clinic patients.

Vitamin tested	Patients tested	Patients deficient	Percent deficient
B1	126	9	7.1%
B6	128	48	37.5%
B12	116	20	17.2%
D (25-(OH)D)	117	43	36.8%

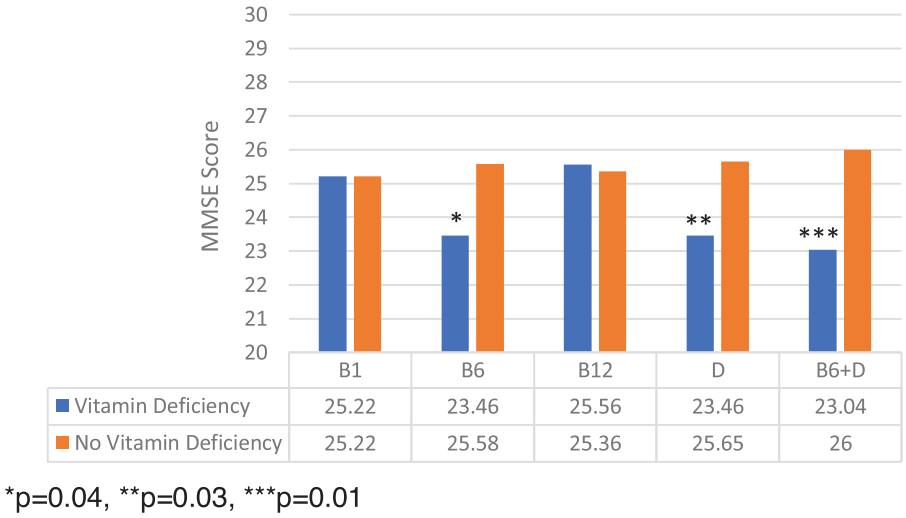

FIGURE 1 Mini Mental State Examination (MMSE) MSE and vitamin deficiency.

in both vitamins (odds ratio [OR] = 6.911; 95% confidence interval [CI] = 2.785, 17.150; $p < 0.001$).

MMSE scores were examined based on vitamin B1, B6, B12, and D deficiencies. Among those with vitamin B1 and B12 deficiencies, there were no significant differences in the MMSE scores (see Figure 1). A significant difference was noted in MMSE scores for vitamin B6 only and vitamin D only, and this significant difference remained when the vitamin B6 and D deficiency groups were combined. Individuals that did not have a vitamin B6 and D deficiency had a mean MMSE score of 26 (SD = 4.29), whereas those with a deficiency in both vitamins B6 and D had a mean MMSE score of 23.04 (SD = 5.19), and this difference was significant, $t(68) = 3.7$, $p = 0.01$.

4 | DISCUSSION

In this geriatric population presenting for the initial memory clinic evaluation, patients were found to be most commonly deficient in two vitamins rarely assessed in memory patients, B6 and D. Vitamin B12 is assessed routinely in this population but was found to be deficient in only 17.2% of patients, less than half that of vitamins B6 and D.

Vitamin B6 is required for the synthesis of the neurotransmitters serotonin, norepinephrine, epinephrine, and γ-aminobutyric acid(GABA), and as such is involved in both neuronal excitation and inhibition.[5] It has been reported previously that pyridoxine (vitamin B6) and pyridoxal phosphate deficiencies are associated with insomnia.[13-15] This is important because sleep is critical for normal cognition and prevention of AD.[2] The potential connection between vitamin B6 and cognition has been reported previously in kidney transplantation patients with mild cognitive impairment.[16] Although folate and vitamin B12 were rarely found to be deficient, vitamin B6 deficiency affected 44% of the patients with kidney transplants.

It has been reported that serum vitamin D levels are decreased significantly in patients with mild cognitive impairment and AD compared to healthy controls.[17] There is evidence that polymorphisms in the vitamin D receptor gene are associated with AD.[18] Vitamin D also modulates proinflammatory states and reduces the burden of amyloid beta (Aβ) plaque.[19] Calcitriol, an active vitamin D metabolite, has been shown to act in the blood mononuclear cells of patients with AD to promote Aβ plaque phagocytosis.[20]

The positive association between vitamin B6 and D deficiencies is particularly intriguing, since they are from different nutritional sources. Furthermore, vitamin B6 is water soluble, whereas vitamin D is fat soluble. There is a higher risk (OR = 6.91) that vitamin B6 and D deficiencies will occur together warranting the recommendation that if one of these vitamins is found to be deficient, the other vitamin level should be evaluated.

Previous studies suggest that both vitamins B6 and D are important for cognition, a finding supported by this study. A deficiency of either vitamin B6 or D was found to be associated with significantly lower MMSE scores. A prior study of memory clinic patients in northern Wisconsin reported a significant positive correlation between vitamin D levels and MMSE scores.[7] This significant MMSE score difference is remarkable, and to our knowledge is unreported for any reversible factor affecting cognition.

A primary limitation of this cross-sectional retrospective study design is that it does not allow for causal inferences or provide further insight into the association between vitamin levels and cognitive disturbances. In addition, patients were not fasted prior to vitamin level assessment because fasting would not be desirable to do prior to a cognitive assessment should hypoglycemia be produced. Lack of fasting could have impacted vitamin B6 levels, which is ideally tested after an 8 hour fast. Because we were looking for a deficiency rather than toxic vitamin B6 levels, this could have led to an underestimation of the prevalence of B6 deficiency, and, therefore, does not detract from the significance of our findings. Another limitation of the study is the lack of diversity within the population; 96% of the population reported their ethnicity as White.

Routine testing for vitamin B6 and D deficiencies could lead to repletion that would potentially improve cognitive performance and

increase the likelihood of effective medical treatment. This is particularly relevant now, since the MMSE score is used to qualify patients with AD for treatment with the new disease-modifying therapies, and patients with a vitamin B6 or D deficiency could fall below the allowable MMSE score for treatment in part due to this deficiency.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Consent was not necessary for this study, and IRB approval as an exempt study was documented.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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