ORIGINAL RESEARCH

Hypovitaminosis D in Delirium: a Retrospective Cross-sectional Study

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ABSTRACT

Background

As vitamin D may have a neuroprotective effect, the authors studied the association of biomarkers of vitamin D status and delirium to see if low vitamin D status was common in delirium cases.

Methods

Biochemical measures of vitamin D (25-hydroxyvitamin D [25-OHD]) and calcium metabolism were used in this retrospective cross-sectional analysis of adult in-patients with delirium, admitted at three Canadian academic hospitals from January 2011 to July 2012. Primary outcome was to determine estimates of the prevalence of hypovitaminosis D in this group in whom vitamin D was checked.

Results

Seventy-one (5.8%) out of 1,232 delirium inpatients had their vitamin D measured. Thirty-nine (55%) showed vitamin D insufficiency (25-OHD of 25-75 nmol/L) and 8 (11%) showed vitamin D deficiency (25-OHD < 25 nmol/L). Mean serum 25-OHD levels were lower in males (57.1±7.7 nmol/L) than in females (78.2±6.1 nmol/L), $p = .01$, even when controlled for age and season. Men were younger than the women (74.4±2.3 vs. 82.4±1.7, $p = .005$). Mean age was 78.7±1.5 years, and 33 (47%) were male.

Conclusions

Although vitamin D is rarely checked during delirium workup and/or management, high rates of hypovitaminosis D were found to be common in the delirium in-patients in whom it was checked. Larger studies would be needed to estimate the prevalence of hypovitaminosis D in delirium and whether hypovitaminosis D plays a role in the pathogenesis of delirium.

Key words: delirium, vitamin D, vitamin D insufficiency, acute in-patient, acute care

INTRODUCTION

Delirium is common in hospitalized patients. A recent review has revealed a rate of 11% to 42% in general medical in-patients.(1) On surgical wards the incidence of post-operative delirium ranges from 9 to 87%.(2) Delirium is associated with increased morbidity, mortality, and cost of care, including an increased hospital length of stay (LOS).(1,3,4) If recognized and treated appropriately, the burden of illness conferred by delirium can often be minimized. As such, identification of plausible delirium risk factors which are easily reversed is a clinical imperative. This is especially important if there is a readily available biomarker for a putative delirium risk factor.

Vitamin D is a secosteroid hormone in its active metabolite form, with actions on the central nervous system (CNS).(5,6,7) It circulates in blood as calcidiol (25-hydroxyvitamin D).(5) Since the role of vitamin D on brain function has become more explicit, clinicians and researchers have speculated that hypovitaminosis D may be important in the pathogenesis of delirium.(8,9) Low levels of vitamin D are also associated with various morbidity and mortality rates, but causality has not yet been determined.

Vitamin D crosses the blood–brain barrier by a combination of passive diffusion and active transport (via carriers in cerebral capillaries and the choroid plexus).(10) Vitamin D exerts its CNS action through the vitamin D receptor (VDR), which is located in the hippocampus, hypothalamus, cortex, and subcortex(6,11,12) —neuroanatomic areas that subserve cognition. Calcitriol (1,25-dihydroxyvitamin D), the active

form of vitamin D, regulates calcium homeostasis[13] and reduces oxidative stress in hippocampal neurons.[14] Vitamin D regulates genes that synthesize cell products, thus demonstrating autocrine and paracrine activity.[15] Moreover, vitamin D promotes neuroprotection by modulating the production of choline acetyltransferase.[16] As choline acetyltransferase is the key enzyme in biosynthesis of acetylcholine and cholinergic deficits are implicated in delirium, it has been speculated that vitamin D may thus play a role in protecting the brain from delirium.[3,17]

Predisposing cognitive risk factors for delirium are also common manifestations of hypovitaminosis D.[3] Substantial evidence for a link between cognitive impairment and hypovitaminosis D has already been described.[7,18,19,20] Proposed neuropsychiatric correlates of vitamin D deficiency include impairments in executive functions, particularly in mental shifting and information updating.[7] A recent study by Masoumi *et al*.[21] demonstrated that 1,25-dihydroxyvitamin D strongly stimulated beta-amyloid phagocytosis and subsequent clearance providing protection against cellular apoptosis, known to be important in the pathogenesis of Alzheimer's disease. Despite the substantial theoretical basis for a link between vitamin D and delirium, to date there has been only a limited exploration of this association. A recent study on critically ill delirious patients in the ICU found no association between vitamin D level and development of delirium.[22] However, the authors acknowledged limitations of the study, including a sample drawn only from the medical intensive care unit and part of a larger study of patients with acute respiratory distress syndrome (ARDS). It is worthwhile to fully investigate any association between vitamin D and delirium in various settings since vitamin D status could represent a potentially reversible and easily treatable risk factor for delirium.

METHODS

We conducted a retrospective cross-sectional analysis of adult in-patients diagnosed with delirium at three academic medical centres in Hamilton, Ontario, by extracting electronic data systematically from medical records, which used *The International Classification of Diseases*, Tenth Revision (ICD-10)[23] as the local coding system. Eligible cases were defined as any medical or surgical in-patient age 18 years or older who received a discharge diagnosis of delirium between January 1, 2011 and July 31, 2012, as coded F05.0 (delirium not superimposed on dementia), F05.8 (other delirium, mixed or post-operative type), F05.9 (delirium, unspecified), and F10.4 (mental and behavioural disorders due to use of alcohol/withdrawal state, with delirium). Cases that had an available serum 25-OHD level during the same admission were included. Primary outcome was to determine estimates of the prevalence of biomarkers of vitamin D status and calcium homeostatic indicators, while secondary outcomes were to determine seasonal effects on vitamin D levels, and clinical and demographic correlates in those included. Subsequently, serum 25-OHD, total calcium, magnesium, phosphate, and intact parathyroid hormone (PTH) values were extracted. Local laboratory reference values were used for vitamin D insufficiency (defined as 25-OHD of 25-75 nmol/L) and vitamin D deficiency (defined as 25-OHD < 25 nmol/L). Additional data collected for analysis included clinical co-morbidity with dementia, based on the ICD-10 code F05.1 (delirium superimposed on dementia), and demographic information. Season that vitamin D was sampled was coded as "dark" (during the months of October to March) and "light" (April to September), to control for the time of year as a confounding variable.

These data were obtained from the institution's medical archival retrieval system, which contains integrated data from laboratory, administrative, and other databases within our health system. All patient information was de-identified by a neutral mediator. Descriptive analyses generating means and standard error of the mean (SEM) for continuous data and proportions for categorical data were conducted. Significance was determined to be $p < .05$. Population was stratified by gender, vitamin D categories, and presence/absence of dementia, and means were compared across these categories using ANOVA; biochemical tests performed were also compared across these groups while controlling for potential confounders (ANCOVA). Pearson correlations were performed to determine which variables were associated with which. Both stepwise and multiple linear and logistic regression analyses were performed generating models predicting linearly for LOS and logistically for vitamin D deficiency. All of these statistical analyses were done using SAS version 9.2 (SAS Institute Inc., Cary, NC). This study was approved by the university's institutional ethics review board and deemed to be exempt from patient informed consent.

RESULTS

A total of 71 (5.8%) delirium in-patients had documented serum 25-OHD levels and thus met criteria for inclusion. Only 14 (20%) of these constituted surgical cases; 14 (20%) had a pre-morbid dementia diagnosis. Mean LOS for patients in the sample was 36.5±4.7 (range, 3–221) days. Mean age was 78.7±1.5 (range, 47–98) years, and 33 (47%) were male (Table 1). Thirty-nine (55%) of the sample showed vitamin D insufficiency with a mean serum 25-OHD level of 51.8±2.0 (range, 30.5–69.1) nmol/L, and 8 (11%) met criteria for vitamin D deficiency with a mean serum 25-OHD level of 20.8±0.8 (range, 17.3–23.7) nmol/L (Table 2). An additional analysis comparing population characteristics across the study populations revealed that sample men were younger than sample women (74.4±2.3 vs. 82.4±1.7; $p = .005$). Mean serum 25-OHD levels were lower in males (n = 33; 57.1±7.7 nmol/L) than in females (n = 38; 78.2±6.1 nmol/L), $p = .01$, even when controlled for age and season ($p = .04$). There was no effect of "light" season (68.9±6.14) compared with

"dark" season (68.0±7.3) on vitamin D levels. Although still within normal range, subjects with co-morbid dementia had higher mean serum calcium levels (2.41±0.13) compared to the non-dementia subgroup (2.19±0.02), $p = .01$ (Table 3).

DISCUSSION

Understanding contributing factors to delirium may potentially aid in improving the prevention and/or management of this often under-recognized condition. The appropriate normative range for serum 25-OHD has constituted a controversial and important issue. Nevertheless, historical normative data may underestimate circulating levels of 25-OHD expected in patients with sufficient vitamin D.[24] Given the absence of assay standardization and the lack of consensus regarding clinical cut-off values, reference ranges must remain laboratory-specific.[25] Thus, high rates of suboptimal vitamin D levels in delirium in-patients in whom vitamin D status was checked were found in this retrospective sample. Serum concentration of 25-OHD, a biomarker of exposure but unclear to what extent serving as a biomarker of effect, is the best indicator of vitamin D status.[26] It reflects vitamin D produced exogenously (e.g., natural sources, fortified foods, and supplements), and endogenously when the skin is exposed to UVB rays,[26] and has a fairly long circulating half-life of 14-21 days.[27] People living above the latitude of 33° North will receive sufficient solar radiation only between 10:00 a.m. and 3:00 p.m. from April to September.[28] Aside from sunlight deprivation, other factors associated with vitamin D insufficiency include inadequate nutritional status, darker skin pigmentation, sunscreen use, aging and age-related dermatological changes, impaired renal function, and malabsorption syndromes.[5]

In the current study, vitamin D was checked in only about 6% of all delirium cases, suggesting that vitamin D was rarely checked in delirium workup and/or management. Therefore, physician attitude toward reasons to screen for or quantify serum vitamin D levels may likely have been biased toward the already established evidence not only regarding age (e.g., elderly), but also bone health (e.g., osteoporosis, falls and fracture prevention).[29] Since these medical centres did not have standard "delirium evaluation", standardized clinical pathways, and/or laboratory order sets, physician preference and habit in ordering laboratory studies may be a factor. An

TABLE 1.
Demographics and laboratory values for the study population

Variable	*Mean ± SEM*
Age (y)	78.7±1.5
Length of Stay (d)	36.5±4.7
25-OHD (>75 nmol/L)	68.4±5.0
Total Calcium (2.15–2.55 mmol/L)	2.23±0.03
Magnesium (0.66–1.07 mmol/L)	0.76±0.02
Phosphate (0.80–1.45 mmol/L)	0.99±0.03
PTH Intact (1.5–7.2 pmol/L)	3.2±0.58
Gender (% Male)	47

TABLE 2.
Comparison of means across vitamin D subgroups

Variable	*25-OHD <25 (n=8)*	*25-OHD between 25 and 75 (n=39)*	*25-OHD >75 (n=24)*	$P_r>F$
Age (y)	76.5±2.96	77.1±2.16	82.1±2.25	NS
Length of Stay (d)	23.6±6.2	36.5±5.5	40.9±10.6	NS
Gender (%Male)				NS
25-OHD (nmol/L) ANCOVA (Season, Age)	20.8±0.8	51.8±2.0	111.3±9.0	<0.0001 <0.0001
Total Calcium (mmol/L) ANCOVA (Season, Age)	2.06±0.05	2.23±0.03	2.3±0.08	NS (0.07) NS
Magnesium (mmol/L) ANCOVA (Season, Age)	0.80±0.06	0.75±0.02	0.77±0.02	NS NS
Phosphate (mmol/L) ANCOVA (Season, Age)	0.98±0.10	0.99±0.04	0.98±0.05	NS NS
%Season				
Light	25	43.6	41.7	NS
Dark	75	56.4	58.3	

TABLE 3.
Comparison of means across existing diagnosis of dementia or no dementia

Variable	*Dementia Absent (n=57)*	*Dementia Present (n=14)*	$P_r>F$
Age (y)	78.0±1.66	81.6±3.04	NS
Length of Stay (d)	35.5±4.8	40.8±14.3	NS
Gender (%Male)	44	57	NS
25-OHD (nmol/L)	67.1±4.7	73.5±16.9	NS
ANCOVA (Age, Season)			NS
Total Calcium (mmol/L)	2.19±0.02	2.41±0.13	0.01
ANCOVA (Age, Season)			0.01
Phosphate (mmol/L)	0.97±0.03	1.07±0.09	NS
ANCOVA (Age, Season)			NS
Magnesium (mmol/L)	0.76±0.02	0.76±0.03	NS
ANCOVA (Age, Season)			NS
%Season			
Light	42.1	35.7	NS
Dark	57.9	64.3	
% Vit D deficiency (<25)	10.5	14.3	NS

additional study could be to look for the incidence of delirium in a large cohort selected primarily for low vitamin D levels. While our sample only contained nine patients under the age of 65 years, it is worth noting that over half of these patients showed vitamin D insufficiency. Since the assay is expensive and supplementation is safe, vitamin D deficiency is typically due to inadequate intake (in the absence of malabsorption); therefore, vitamin D supplementation should be routinely addressed when in the absence of a confirmatory laboratory assay in frail patients.

Given the reports of hemodilution affecting vitamin D levels,[30] reassessment of vitamin D status post-delirium recovery with normalized renal/fluid status, may be important to ascertain the true vitamin D status in a period of hemodynamic and metabolic stability. This may be especially important with delirium associated with acute renal failure.

Significantly more delirious men were found in the vitamin D inadequacy range. Previous research has also shown a higher prevalence of vitamin D deficiency among men as compared to women,[31] perhaps due to gender differences in the amount of body fat and/or its distribution. Although the role of vitamin D in delirium is yet undetermined, physicians should be mindful of the gender differences concerning vitamin D status in men. Despite previous literature on seasonal effects on vitamin D levels, with lower concentrations in the winter than in the summer,[32] our findings, although carried out in a small sample size, did not support any effect of season on the vitamin D status. Perhaps our sample of delirium patients was representative of those with multiple medical co-morbidities as patients prone to delirium often have, which restricts their outdoor access and does not produce a seasonal variation in the vitamin D levels. This could also mean the seasonal variation in vitamin D levels is less important in delirium cases than in other clinical scenarios. Additionally, malnutrition was found to be prevalent in older adults with hypovitaminosis D.[33] As malnutrition may further enhance the risk for delirium, it would be advisable to measure vitamin D levels at admission, so that corrective action of supplementation of low vitamin D status can be accomplished. However, in institutions where the vitamin D assay cannot be obtained due to expense and/or other logistical barriers, vitamin D supplementation can be initiated on clinical grounds alone.

As the precise role for vitamin D screening has not been established, given the low vitamin D status in our delirium cases on whom this was checked, further monitoring and perhaps supplementation appears reasonable. While this study provides some insight into potential vitamin D as a factor affecting delirium among medical and surgical inpatients, its retrospective design is an inherent limitation. A cross-sectional study was also limited, as it was carried out at one time during an admission period and gave no indication of the sequence of events—whether a low vitamin D level occurred before or during admission for delirium; thus, it was impossible to infer causality. All factors known to contribute to hypovitaminosis D could not be included in our model due to the availability of information in our data repository. For example, environmental factors, nutritional status, race, hemodynamics, and medications and supplements were not accounted for in our study. Another limitation is that the authors explored delirium in one setting (in-patient). Although a causal attribution between low vitamin D and delirium cannot be established in light of the cross-sectional nature of our study, the results, at least, argue for the potential importance of identifying the effect of vitamin D in all-age delirium patients, particularly in younger adults, which were underexplored in our study. Inasmuch as vitamin D is easily replaced, if our study is validated by larger, prospective studies, it could represent a reversible risk factor for delirium. Additional well-designed prospective cohort studies in in-patient units may determine if vitamin D is a biomarker of effect specific enough in delirium to argue for screening of vitamin D status in all delirium patients as part of the routine workup, and subsequent required supplementation during the management of delirium and post-delirium care.

CONCLUSION

Our study demonstrated hypovitaminosis D in 66% of delirium cases where a vitamin D level was assessed on in-patient services at three academic medical centres. Whether or not low vitamin D represents an independent risk factor for the development of delirium would require prospective studies. If our findings are validated and replicated by larger,

prospective study designs, more routine assessment of vitamin D status (with a willingness to supplement vitamin D in cases of insufficiency/deficiency) could become part of the clinical management of delirium. Larger studies of vitamin D status in known delirium cases and prevalence studies of delirium in cases of known hypovitaminosis D would be helpful to elucidate the possible relationship between hypovitaminosis D and delirium.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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