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Low Vitamin D Levels Are Common in Patients with Epilepsy

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SUMMARY

Purpose—Vitamin D is important for bone health, and vitamin D deficiency may contribute to other disorders (e.g., autoimmune, infections, cancer, degenerative, diabetic, and vascular).

Enzyme-inducing antiepileptic drugs have been particularly implicated for osteoporosis risk given their effects on vitamin D. We examined the prevalence of vitamin D deficiency in adult epilepsy patients.

Methods—We conducted an observational study of consecutive epilepsy patients treated by two clinicians at the Emory University Epilepsy Center from 2008 to 2011 in order to determine the frequency of low vitamin D levels and possible differential antiepileptic drug risks. Vitamin D 25-OH levels were categorized as low (<20ng/ml), borderline (20–29ng/ml), or normal (>30ng/ml). Antiepileptic drugs were categorized based on their enzyme inducing properties. Descriptive and inferential statistics were employed.

Results—Vitamin D levels were obtained on 596 patients with epilepsy. Mean age was 41 years (SD = 14; range = 18–81); 56% were women. Race/ethnicity was 55% Caucasian, 34% Black, 2%

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Author Contributions.

Ms. Teagarden helped draft the manuscript, collected the data, and supervised the study. Dr. Meador contributed to study design and helped draft the manuscript. Dr. Loring contributed to study design, conducted the statistical analyses, and revised the manuscript.

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Asian, and 7% Unknown. The mean vitamin D level was 22.5 (SD = 11.9; range = <4 to 98), and 45% had level <20ng/ml. Mean vitamin D levels ($F=6.48$, $p=.002$) and frequencies of vitamin D categories ($p=.002$, Chi Square test) differed across the antiepileptic drug groups. Vitamin D deficiency was present in 54% of enzyme-inducing and 37% of non-enzyme-inducing antiepileptic drugs groups.

Conclusions—Vitamin D deficiency is common in patients with epilepsy on antiepileptic drugs. Monitoring of vitamin D should be considered as part of the routine management of patients with epilepsy.

Keywords

Vitamin D; antiepileptic drugs; epilepsy

INTRODUCTION

Vitamin D is a prohormone and not actually a vitamin (DeLuca, 2004). The major source of vitamin D is from exposure to sunlight. Ultraviolet irradiation from sunlight converts 7-dehydrocholesterol to vitamin D₃, which is biologically inert. Vitamin D₃ is metabolized in the liver to 25-hydroxyvitamin D, and then metabolized in the kidney to 1 α ,25-hydroxyvitamin D, which is the active metabolite that functions via an intracellular receptor, which is present in many different bodily tissues (DeLuca, 2004; Rosen et al., 2012a).

Vitamin D is important for bone health. The widespread distribution of vitamin D receptors across many tissues suggests that vitamin D may possess multiple physiological actions (Rosen et al., 2012a). In addition to osteoporosis and rickets, vitamin D deficiency has been suggested to possibly contribute to conditions such as autoimmune disorders (e.g., multiple sclerosis, rheumatoid arthritis), cancer, chronic fatigue, depression, falls in the elderly, diabetes, vascular disorders (e.g., heart disease, stroke), neurodegenerative disorders, and epilepsy (DeLuca, 2004; Rosen et al., 2012a; Holick et al., 2011; Ganji et al., 2010; Holló et al., 2013). Antiepileptic drugs (AEDs), especially enzyme inducing AEDs (EIAEDs), have been associated with reduced bone mineral density and fracture risk (Lee et al., 2010; Nakken and Taubøll, 2010). One contributing factor may be the effects of AEDs on vitamin D metabolism (Lee et al., 2010; Nakken and Taubøll, 2010). Six cohort studies in children with epilepsy have found vitamin D deficiency ranging from 4–75%, and six studies of vitamin D therapy in children with epilepsy have shown positive effects on bone mineral density or bone biomarkers (Harijan et al., 2013). Vitamin D status in adults with epilepsy is less clear. Several studies have failed to find that patients on EIAEDs have lower vitamin D levels than those on non-enzyme-inducing AEDs (Non-AEDs) (Vestergaard, 2005; Pack et al., 2005; Pack et al., 2011a), and a recent systematic review found insufficient evidence to determine if AEDs alter serum 25-hydroxyvitamin D levels (Robien et al., 2013). The prevalence of vitamin D deficiency in adults with epilepsy and its relationship to specific AEDs remain uncertain.

METHODS

Design

The study was a retrospective chart review.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Emory Institutional Review Board (IRB). Waiver of consent was granted for this retrospective chart review.

Participants & Procedures

We noted a high number of patients with low vitamin D levels in our epilepsy clinic, so vitamin D levels are routinely obtained as part of our standard clinical care for patients with epilepsy. After IRB approval, medical charts from January 1, 2008 to July 31, 2011 were reviewed for people with epilepsy on antiepileptic drugs (AEDs) followed in the Emory Epilepsy Center by two of the investigators (DT, KM). The patients included were a consecutive series. Information was collected on vitamin D levels and date drawn, AED use at time of vitamin D level, age, gender, and race/ethnicity. Vitamin D levels (i.e., 25-hydroxyvitamin D) were categorized: low (<20 ng/ml), borderline (20–29 ng/ml), and normal (≥ 30 ng/ml) (Holick et al., 2011). Note that all the vitamin D levels were obtained from the same lab using the same assay. None of the patients had renal failure or pre-existing known bone disease. AEDs were categorized as: EIAEDs (eg, carbamazepine, phenobarbital, phenytoin, primidone), Weak EIAEDs (eg, oxcarbazepine and topiramate since these AEDs produce weaker enzyme induction which is probably significant at higher dosages), or Non-EIAEDs (eg, gabapentin, lamotrigine, levetiracetam) (Johannessen and Landmark, 2010).

Statistical Analysis

Descriptive and inferential statistics were employed. Statistical analyses were conducted with ANOVA for vitamin D levels and also with non-parametric Chi Square contingency tables for frequent data comparing AED as a function of enzyme induction action.

RESULTS

The total sample included 596 patients with mean age = 41 years (standard deviation = 14; range = 18–81), 56% women. Race/ethnicity were 55% Caucasian, 34% Black, 2% Asian, 2% Hispanic, and 7% Unknown. 38% were obese as defined as body mass density ≥ 30 kg/m². Epilepsy types were: focal = 70% (n = 420), generalized = 21% (n = 127), unknown = 8% (n=49). AED monotherapy was used in 59%.

Mean Vitamin D level = 22.5 ng/ml (standard deviation (SD) = 11.9; range = <4 to 98). Overall 45% had a level <20ng/ml, and 11% had a level <10ng/dl. Significant differences were seen across the three AED groups (i.e., EIAED, Weak EIAED, Non-EIAED) for mean vitamin D level [F (2,593) = 6.38, p = .002] and for vitamin D category (<20ng/ml, 20 to <30 ng/ml, and ≥ 30ng/ml) [Chi Square = 16.4, p = .002]. See Table 1 for additional details. Vitamin D levels did not differ across epilepsy types [F (2, 593) = 1.61, p = .20] or between

monotherapy and polytherapy patients [$F(1, 594) = 0.15, p = .70$]. Vitamin D levels were lower in Blacks (mean = 18.9, SD = 11.8) vs. Caucasians (mean = 25.1, SD = 11.9) [$F(1, 529) = 34.34, p = .000$]. EIAED groups did not differ by race [Chi-square = 1.3, $p = .52$]. Vitamin D levels for October-March (mean=21.2, SD=12.0) were lower than April-September (mean=24.1, SD=11.7) [$F(1, 593) = 8.95, p = .003$]. Vitamin D levels were lower in women (mean=21.4, SD=11.9) vs. men (mean=23.9, SD=11.8) [$F(1, 594) = 6.68, p = .01$], and lower in obese (mean=19.8, SD=10.7) vs. non-obese (mean=24.1, SD=12.3) patients [$F(1, 589) = 19.08, p = .000$]. Those who reported that they were receiving supplements with vitamin D (28%, $n = 165$) had higher vitamin D (mean=36.4, SD=11.0) than those not on supplement (mean=17.1, SD=6.9) at baseline [$F(1, 594) = 652.59, p = .000$].

DISCUSSION

The primary finding in this study is that vitamin D deficiency is common in adult patients with epilepsy treated with AEDs. Mean vitamin D levels and the frequency of vitamin D deficiency differed across AEDs. Although we found that vitamin D deficiency is more frequent in those on EIAEDs, it is also common in patients on Non-EIAEDs. Vitamin D levels in our patients are lower in blacks than Caucasian, in the fall/winter than spring/summer months, in women vs. men, in those on no vitamin D supplements, and in the obese, similar to the general population (Kumar et al., 2009).

Osteoporosis is increased in patients with epilepsy (Pack et al., 2003; Lado et al., 2008), and reports of the relative risk vary from 1.7 to 3.8 (Lazzari et al., 2013). Patients with epilepsy are two to six times more likely to suffer fractures (Nakken and Taubøll, 2010; Souverein et al., 2006; Shiek Ahmad et al., 2012). Factors contributing to this risk are multifactorial including seizures, impaired balance, inactivity, low bone mineral density, inadequate calcium intake, and AED use (Pack et al., 2011b). Fractures, which are directly related to seizures, comprise only a minority of fractures in patients with epilepsy. AED-related risk factors for osteoporosis include longer duration of AED therapy, polytherapy regimen, and use of EIAED although Non-EIAEDs may affect bone health (Shiek Ahmad et al., 2012; El-Hajj Fuleihan et al., 2008). Even though risk increases with duration of AED treatment, reduced bone mineral density can be seen in the first year of AED therapy (Sheth et al., 2008; Pack et al., 2008). Additional well-controlled studies are needed to fully understand the risks and mechanisms of decreased bone density and fractures in people with epilepsy. Direct linkage of vitamin D deficiency to bone fractures may be particularly difficult in epilepsy patients where factors other than vitamin D may affect bone density. Risk of fractures may be increased due to seizures and to reduced coordination from the underlying brain disease or from the AEDs.

Vitamin D status is an important factor contributing to bone health. The frequency of vitamin D deficiency (<20 ng/ml) in our patients with epilepsy (45%) is higher than the general USA population (32%) (Ganji et al., 2012). This difference is present despite the fact that our population is from the southern USA, whereas the general USA population sample also included subjects from more northern latitudes where lower vitamin D levels would be expected. The difference cannot be explained by obesity since the rate of obesity

in our patients (38%) is similar to the general population (35%) (Ogden et al., 2014). Vitamin D deficiency in our patients was higher in EIAEDs (54%) than Non-EIAEDs (37%). It is unclear if the rate for non-EIAEDs is higher than the general population. Some risk factors for vitamin D deficiency include lack of sun exposure, darker skin pigmentation, obesity, malabsorption syndromes, granulomatous diseases (e.g., sarcoid, TB), medications used to treat HIV, and AEDs (Holick et al., 2011). We did not systematically investigate all comorbid conditions that increase the risk of vitamin D deficiency, but the high frequency of vitamin D deficiency in the epilepsy population highlights the importance of screening and appropriate treatment in patients with epilepsy. There appear to be multiple mechanisms underlying the untoward effects of AEDs on bone health (Pack et al., 2011b). However, a randomized control trial has demonstrated that vitamin D supplementation (4,000 IU/day) increases bone mineral density in adult patients with epilepsy (Mikati et al., 2006).

The Endocrine Society's Guidelines recommend evaluation of vitamin D status via serum 25-hydroxyvitamin D levels in individuals at risk for vitamin D deficiency, which includes patients on AEDs (Holick et al., 2011). Although there is controversy as to the definition of vitamin D deficiency and appropriate treatment (Rosen et al., 2012b), the Endocrine Society defines vitamin D deficiency as a 25-hydroxyvitamin D level <20ng/ml (Holick et al., 2011).³ The Endocrine Society recommends that vitamin D deficiency be treated with 50,000 IU of vitamin D once a week for 8 weeks or its equivalent of 6,000 IU per day (i.e., about 67 days) to achieve a blood 25-hydroxyvitamin D level >30ng/ml (Holick et al., 2011). This should be followed by 1,500 – 2,000 IU per day maintenance therapy (Holick et al., 2011). In addition, calcium intake should be optimized and be 1,000 – 1,200mg total calcium per day. In the general population, supplementation with vitamin D and calcium can reduce the risk of fractures (Tang et al., 2007; Avenell et al., 2009).

Beyond bone health, several studies have suggested that vitamin D deficiency may contribute adversely to autoimmune disorders (e.g., multiple sclerosis, rheumatoid arthritis), cancer, chronic fatigue, depression, diabetes, vascular disorders, and neurodegenerative disorders (DeLuca, 2004; Rosen et al., 2012a; Holick et al., 2011; Ganji et al., 2010). Further, animal and human studies suggest that vitamin D deficiency may worsen seizures (Holló et al., 2013). Additional research is needed to confirm these observations.

Presently, there are no guidelines for assessment of vitamin D and bone health in patients with epilepsy other than the Endocrine Society's recommendation to screen vitamin D levels in patients on AEDs. Although additional research is needed to assess the utility of vitamin D and calcium supplementation, we feel that the intake of calcium and vitamin D should be optimized in all persons with epilepsy treated with AEDs given the higher risk of osteoporosis and fractures in this population. In view of the high prevalence of vitamin D deficiency in our large sample of epilepsy outpatients, we propose that all patients with epilepsy should be screened who have not already been screened and treated appropriately. In those with vitamin D deficiency, weight reduction and weight bearing exercise should be recommended. Assessment of bone mineral density using dual energy x-ray absorptiometry should be considered in patients with vitamin D deficiency to diagnose significant osteoporosis and direct anti-osteoporotic treatment. Dual energy x-ray absorptiometry might also be considered in patients taking AEDs for 3–5 years since osteoporosis can occur with

normal vitamin D levels (Herman, 2009). In conclusion, since vitamin deficiency is common in patients with epilepsy and may contribute at least in part to the increased risk of fractures in this population, monitoring of vitamin D should be considered as part of the routine management of patients with epilepsy.

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Highlights

- Antiepileptic drugs may affect vitamin D and bone health.
- Prevalence of vitamin D deficiency in epilepsy patients is unknown.
- Vitamin D deficiency was present in 45% of patients on antiepileptic drugs.
- Vitamin D deficiency is common in patients with epilepsy on antiepileptic drugs.
- Monitoring of vitamin D should be part of routine management of epilepsy.

Table 1

Sample sizes, mean (standard deviations) for vitamin D levels (i.e., ng/ml of 25-hydroxyvitamin D), and % distributions across vitamin D ranges for antiepileptic drug groups.

	EIAEDs	Weak EIAEDs	Non-EIAEDs	Total Sample
n	196	115	285	596
Mean Vitamin D	20.5 (11.3)	21.5 (12.0)	24.3 (12.1)	22.5 (11.9)
% <20 ng/ml	54%	50%	37%	45%
% 20–29 ng/ml	29%	29%	33%	31%
% ≥ 30 ng/ml	18%	21%	30%	24%

n = number; % = percent; EIAEDs = enzyme inducing antiepileptic drugs (e.g., carbamazepine, phenobarbital, phenytoin, primidone); Weak EIAEDs = weak EIAEDs (e.g., oxcarbazepine and topiramate); Non-EIAEDs = non-enzyme-inducing AEDs (e.g., gabapentin, lamotrigine, levetiracetam).