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Prevalence and risk factors for vitamin D insufficiency among children with epilepsy

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Abstract

This cross-sectional study was designed to determine the prevalence of, and risk factors for, vitamin D insufficiency among children treated for epilepsy in a general pediatric neurology clinic. Children with epilepsy, aged 3–17 years, treated by the authors between September 2008 and March 2009, were included. Vitamin D levels and relevant risk factors were evaluated using multiple logistic regression. 78 patients (41% male, 81% Caucasian) with mean age 11.64 ± 4.37 years were included. 25% had 25-hydroxy vitamin D levels $< 20\text{ng/ml}$. Only the top 25% of children had levels considered to be normal ($> 32\text{ng/ml}$). Girls and children with elevated body mass index were at increased risk for low 25-hydroxy vitamin D (odds ratio of low 25-hydroxy vitamin D was 4.07 for girls vs. boys, 95% confidence interval, 1.18–13.97; odds ratio 1.179, 95% confidence interval 1.047–1.329 for each 1-unit increase in body mass index). Use of newer antiepileptic drugs was not associated with altered risk, compared to older enzyme-inducing drugs. Vitamin D insufficiency was highly prevalent in this unselected population of children with epilepsy. Female gender and increased body mass index were significant risk factors for low vitamin D levels, while antiepileptic drug regimen was not.

Keywords

vitamin D; 25-hydroxy vitamin D; cholecalciferol; epilepsy; antiepileptic drugs

Introduction

Both the lay press and medical literature have recently focused attention on the impact of vitamin D on various aspects of health. The association between vitamin D, antiepileptic drugs (AEDs), and bone health in individuals with epilepsy has been recognized for more than thirty years [1]. Although few comparable data are available for children, adults with epilepsy are known to be at significantly increased risk for bone fractures, compared to the general population; increasing age and duration of treatment are important risk factors [2–4].

The issue of bone health in children with epilepsy is particularly important, as these patients are often with AEDs treated for many years, including the time of highest bone mineral accrual. Seizures themselves pose a risk for injury, including fractures, and the added co-morbidity of

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poor bone health increases this risk, especially in children whose seizures have major motor manifestations, as well as those with impaired motor function and coordination.

Many AEDs are inducers of hepatic CYP450 metabolism. It has been postulated that these AEDs result in increased hepatic metabolism of vitamin D, leading to abnormally enhanced bone turnover. However, non-enzyme inducing AEDs (e.g. valproic acid) have also been associated with poor bone health[5,6]. Therefore, although the newer AEDs (e.g. lamotrigine, levetiracetam, oxcarbazepine) are less-potent enzyme inducers than carbamazepine or phenytoin, they are not necessarily inert in bone metabolism.

Studies have reported variable changes in bone mineral density and vitamin D levels in children taking antiepileptic drugs (AEDs)[7–14]. However, few have examined cohorts of children with epilepsy who are treated with newer AEDs. We aimed to describe the prevalence of, and risk factors for, vitamin D insufficiency among children with epilepsy treated in a general pediatric neurology clinic.

Methods

The study was approved by the Institutional Review Board of the University of Michigan Medical Center. A waiver for informed consent was obtained. All children 3-to-17 years of age with epilepsy treated by the authors were screened on a clinical basis for hypovitaminosis D between September 2008 and March 2009. Levels were drawn in autumn and winter months to decrease variability due to seasonal changes in sunlight exposure. Subjects were residents of the states of Michigan, Ohio, and Indiana. No subject had underlying metabolic bone disease, significant renal impairment, or endocrine disorders. Subjects were not selected for particular epilepsy syndromes, cognitive ability, or motor impairment. These patients' charts were systematically reviewed and vitamin D levels and risk factors were evaluated using multiple logistic regression. We examined potential risk factors for hypovitaminosis D, including type of epilepsy, seizure control, AED regimen (specific medications, polypharmacy vs. monotherapy, duration of treatment), cerebral palsy, ambulatory status, intellectual disability, body mass index (BMI), gender, and ethnicity.

“Old” AEDs included carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and valproate. “New” AEDs included felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, and zonisamide. Carbamazepine, phenobarbital, and phenytoin were considered enzyme-inducing AEDs and the others were not. Patients treated with more than one AED were classified as taking “old” or “enzyme-inducing” AEDs if at least one of their prescribed medications fell into these categories.

Statistical analyses were performed using SAS 9.1.2 (SAS Institute, Inc, Cary North Carolina). Multiple logistic regression used a dichotomous outcome of 25-hydroxy vitamin D (25OHD) less than or greater than 25ng/ml, the normal value in our laboratory. Newer literature suggests that a truly normal 25OHD level is greater than 32ng/ml [15,16], because parathyroid levels begin to rise at lower 25OHD levels. However so few of our patients' levels were this high that we did not have sufficient power to analyze the data using 32ng/ml as the cut-off value.

Results

The demographics of the 78 patients included in the analyses are presented in Table 1. The mean age was 11.64±4.37 years, most of the subjects were Caucasian (81%), and 59% were girls. About half had generalized epilepsy syndromes, while the others had localization-related epilepsy and they had variable seizure-control. The mean 25OHD level was 28.37±14.13ng/ml (25th percentile: 19ng/ml, 75th percentile: 34ng/ml). Five patients (6.4%) had 25OHD levels less than 11ng/ml, in the frankly deficient range. No patient had an abnormal 1,25-

dihydroxyvitamin D level (mean 51.7 pg/mL $\pm$ standard deviation 18.0) and all serum calcium (9.6 mg/dL $\pm$ 0.36), magnesium (4.5 mg/dL $\pm$ 0.8) and phosphorus (2.1 mg/dL $\pm$ 0.2) levels were normal.

In univariate logistic regression analyses, age, body mass index (BMI), epilepsy type (localization-related vs. generalized), and epilepsy etiology (symptomatic vs. idiopathic), were associated with 25OHD levels (all $p < 0.02$). For multiple regression modeling, these variables, as well as season of 25OHD measurement (September-November vs. December-March), intellectual disability, gender, ethnicity, and seizure freedom (vs. continued seizures), were also initially included. These additional variables all had trends toward significant associations with 25OHD ($p < 0.25$) on simple logistic regression and were clinically relevant.

The resultant multiple logistic regression model (Table 2) demonstrated significantly increased odds of low 25OHD levels (defined as < 25 ng/mL, our laboratory's clinical cut-off point for abnormal levels) associated with female gender, localization-related epilepsy syndromes (compared to generalized epilepsy syndromes), as well as increasing BMI. The remaining variables did not contribute significantly to the models and were omitted from the final model.

We then sought to determine whether confounding factors might explain the increased risk of low vitamin D levels among patients with partial seizures. Since valproic acid does not induce hepatic enzymes, and therefore could theoretically reduce the risk of low vitamin D levels, we assessed the use of this AED among patients with localization-related versus generalized epilepsy syndromes. Chi square statistics demonstrated no significant difference in the use of valproic acid between the groups ($\chi^2 = 1.56$, $p = \text{NS}$). However, there was a significant difference in BMI between the two groups, with higher BMI in the patients with localization-related epilepsy (22.0 ± 6.7 vs. 18.8 ± 4.0 , $p = 0.018$). Since increasing BMI was associated with increased risk of hypovitaminosis D, this finding implies that BMI is a confounder in the association of partial seizures (localization-related epilepsy) with low vitamin D levels.

Discussion

Vitamin D insufficiency was highly prevalent among our study subjects. Twenty-five percent of the patients' 25OHD levels were less than 20 ng/mL, and only the top 25% had levels typically considered normal (> 32 ng/mL; the level below which parathyroid hormone levels begin to rise [15,16]). Girls and those with increased BMI were at highest risk for hypovitaminosis D. The data also show higher risk for those with localization-related epilepsy (partial seizures), compared to generalized, but patients with localization-related epilepsy also had statistically higher BMI, thereby confounding this observation.

Although many risk factors for poor bone health among children with epilepsy have been identified, to our knowledge no study has systematically evaluated BMI as a risk factor in this population. However, in the general pediatrics population, obesity is a major identified risk factor for vitamin D insufficiency [17–19]. In a recent study, obesity has been identified as a common co-morbidity in children with newly diagnosed epilepsy [20], with over a third of such children identified as overweight or obese, in comparison with the standard CDC growth curve. Given these data, it is clear that epilepsy patients are not immune from common medical problems of childhood. Additionally, epilepsy and its treatment might interact with general pediatric issues, such as obesity, to increase the risk of poor bone health.

Recent population-based data suggest that the prevalence of hypovitaminosis D in the general pediatric population is high, with 61% of American children having 25OHD levels 15–29 ng/mL and 9% less than 15 ng/mL [21]. Although we did not directly compare our patients' levels with healthy controls, the prevalence in our patients is comparable to these reported data. Of note, most of our patients are non-Hispanic whites, which should place them at lower risk for

vitamin D insufficiency than the general population (African-American and Hispanic American children are at higher risk and are better represented in the national population-based studies). We view the high prevalence of inadequate vitamin D levels in pediatric epilepsy patients as significant, even if the rate is comparable to the general population, since these children are at additional risk for bone injury due to their seizures, comorbid neuromotor dysfunction, and long-term treatment with medications that affect bone health both through vitamin D metabolism and other mechanisms. Screening for and treating low vitamin D levels in pediatric epilepsy patients is inexpensive, lacks significant side effects, and may improve bone health in this vulnerable population.

Nearly half of our patients were treated exclusively with newer AEDs. Since these drugs are not potent hepatic enzyme-inducers, they might reasonably be expected to have a lesser effect on 25OHD levels than traditional enzyme-inducing AEDs. However, analysis of patients on old versus new AEDs in this study showed no difference in their vitamin D levels, either in univariate analyses or after adjusting for other risk factors. Children on either type of AED regimen were at equal risk for low 25OHD levels, albeit approximately equal to the American general pediatrics population. Others have evaluated lamotrigine[6] and oxcarbazepine [22–24] and concluded that these newer drugs may have an impact on 25OHD and/or bone mineral density. Although there has been hope that newer AEDs would have minimal impact on bone health, our data and the available literature on oxcarbazepine and lamotrigine suggest otherwise.

Strengths of this study include the fact that the results represent a true cross-section of patients cared for in a modern academic general pediatric neurology practice, with all 3-to-17-year-old patients treated for epilepsy included in the analyses. This allows for an estimate of the prevalence of vitamin D insufficiency (75% insufficient, using the newer normal value of >32ng/ml[15,16]). In addition, we evaluated their 25OHD levels during the autumn and winter months, to avoid the confounding factor of seasonal variation in 25OHD levels[7,25].

This was a relatively small study, and we risk type II error. However, the fact that so many potential risk factors, including specific AEDs, comorbid cerebral palsy or intellectual disability, and seizure control, did not contribute significantly to the risk of low vitamin D levels is important, because it tells us that as clinicians we cannot a priori reliably predict which of our patients have low vitamin D levels. Traditionally recognized risk factors, such as cerebral palsy, may still be relevant. However, in an era of newer AEDs, this impact might be modulated. Conversely, the increased risks associated with high BMI and female gender are quite significant. Virtually all children with epilepsy may be at risk for hypovitaminosis D. Similarly elevated risk has recently been demonstrated for children with type I diabetes mellitus[26] and systemic lupus erythematosus[27].

We do not routinely screen children with epilepsy with dual energy x-ray absorptiometry scans to evaluate bone mineral density. Therefore, we cannot comment on the impact of our patients' low vitamin D levels on their bone mineralization. However, we postulate that low 25OHD levels should be associated with abnormal bone metabolism and likely places these patients at risk for poor bone health. We also lack systematic dietary assessments and so cannot comment on the impact of our patients' nutritional status on their vitamin D levels. Others have demonstrated that diet has an important effect on vitamin D levels [7] and this should not be overlooked. However, since so many children do not have adequate vitamin D in their diets [17,18,28,29], and in northern climates lack adequate sun exposure for several months of the year, it should not be surprising that the prevalence of vitamin D insufficiency is high. This finding, in combination with the recent increase in the recommended daily vitamin D intake for children [18] suggests that far more of our patients than previously recognized require vitamin D supplementation.

Conclusions

We found vitamin D insufficiency to be highly prevalent among our unselected cohort of children with epilepsy. Potential risk factors for low vitamin D were examined, and female gender and increasing BMI were found to be significant. These are traditionally recognized risk factors in the general pediatric population, but have not been reported among children with epilepsy. For children with epilepsy, cerebral palsy and enzyme-inducing AEDs are often cited as risk factors for poor bone health. We did not replicate these results, but this does not mean that the traditionally recognized risk factors are not important. The high prevalence of hypovitaminosis D suggests that, while being female and having an increased BMI are risk factors, almost all children with epilepsy are at risk. Increased attention on the part of both pediatric neurologists and primary care physicians to vitamin D status and bone health among children with epilepsy is warranted. Further research examining the impact of vitamin D supplementation on bone health in this population is also urgently needed.

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Table 1

Demographic profile of the 78 patients

Variable	N (%)
Total	78 patients
Gender	
Male	32 Male (41%)
Female	46 Female (59%)
Mean Age $\pm$ Standard Deviation	11.64 $\pm$ 4.37 years
Race	
Caucasian	63 (81%)
African-American	8 (10%)
Asian	4 (5%)
Multiracial	1 (1%)
Other	2 (3%)
Seizure Type	
Generalized	38 (49%)
Partial	40 (51%)
Etiology of Epilepsy	
Idiopathic	23 (29%)
Cryptogenic	20 (26%)
Symptomatic	35 (45%)
Seizure frequency	
Seizure-free	31 (40%)
< 1 seizure per month	12 (15%)
1–4 seizures per month	9 (12%)
1 seizure per week	7 (9%)
Daily Seizures	19 (24%)
Anti epileptic drug Therapy	
Monotherapy	43 (55%)
Polytherapy	35 (45%)
Duration of therapy	
<12 months	12 (15%)
12–<24 months	8 (10%)
2–<5 years	22 (28%)
>5 years	36 (46%)
Cerebral Palsy	19 (24%)
Ambulatory	70 (90%)
Intellectual disability	38 (49%)
Tube feeds	8 (10%)
Type of AED*	
Old	Old 17 (22%)
New	New 28 (49%)

Variable	N (%)
Both	Both 23 (29%)

* Old AEDs included: carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, valproate

* New AEDs included: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, zonisamide

Table 2

Results of multiple logistic regression model for 25-hydroxyvitamin D level < 25ng/ml

Parameter	Estimate	Standard Error	p-value	Odds Ratio (95% confidence interval)
BMI [*]	0.1650	0.0608	0.0066	1.179 (1.047–1.329)
Gender ^{**}	−0.7014	0.3148	0.0259	0.246 (0.072–0.845)
Seizure type ^{***}	0.7554	0.2985	0.0114	4.530 (1.406–14.598)

* Modeled for each 1-unit increase in body mass index

** Male versus female (odds ratio for females versus males: 4.07, 95% confidence interval 1.18–13.97)

*** Partial versus generalized seizures