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Original Article

Longitudinal Change of Vitamin D Status in Children With Epilepsy on Antiepileptic Drugs: Prevalence and Risk Factors

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ABSTRACT

BACKGROUND: Our aim was to evaluate the prevalence and risk factors of vitamin D deficiency and the changes of vitamin D level among children with epilepsy on antiepileptic drugs. **METHODS:** The levels of serum 25-hydroxy vitamin D were measured at the start of antiepileptic drugs and at 6- to 12-month intervals in children with epilepsy taking antiepileptic drugs in Pusan National University Children's Hospital. Vitamin D deficiency was defined as 25-hydroxy vitamin D levels <20 ng/mL and insufficiency between 21 and 29 ng/mL. **RESULTS:** A total of 143 children (103 boys and 40 girls) with the mean age of 7.4 ± 5.4 years were included. The mean follow-up duration was 1.8 ± 0.8 years. At the start of antiepileptic drugs and the last follow-up, vitamin D deficiency or insufficiency was recognized in 56.6% (81 of 143) and 79.0% (113 of 143), respectively ($P < 0.01$). The mean value of initial 25-hydroxy vitamin D was 31.1 ± 14.7 ng/mL, which was significantly decreased to 20.2 ± 14.9 ng/mL ($P < 0.01$) in the last follow-up. Polytherapy (−16.0 ± 13.6 ng/mL), longer duration of ≥2 years (−23.5 ± 9.1 ng/mL), tube feeding (−18.2 ± 14.5 ng/mL), and overweight with body mass index of eighty-fifth percentile or greater (−17.0 ± 12.1 ng/mL) had a significant negative effect for the longitudinal change of 25-hydroxy vitamin D. Age, etiologies, seizure outcomes, and type of antiepileptic drugs (enzyme-inducing versus nonenzyme-inducing antiepileptic drugs) did not affect the longitudinal decrease of 25-hydroxy vitamin D. **CONCLUSIONS:** A high proportion of these children on antiepileptic drugs had hypovitaminosis D and a significant decrease between the initial and the last follow-up. Polytherapy and longer duration of antiepileptic drugs, tube feeding, and overweight were independently associated with longitudinally significant decrease of 25-hydroxy vitamin D.

Keywords: vitamin D, hypovitaminosis D, child, epilepsy, antiepileptic drug

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Introduction

There has been increasing concern recently on the impact of vitamin D on human health. Besides rickets and decreased bone mineral density, vitamin D has been related to various disorders, e.g., diabetes mellitus, stroke, autoimmune diseases, and cancer.[1] Causes of vitamin D deficiency are inadequate exposure to sunlight, body mass index (BMI) of >30 kg/m^2, underlying disease (e.g., fat malabsorption syndromes, nephrotic syndrome), and medications including antiepileptic drugs (AEDs).[2] AED medication, particularly long-term therapy or polytherapy, is recognized to be associated with hypovitaminosis D.[3-5] Adults with epilepsy are known to be at considerably increased risk for bone fractures compared with the general population, and increasing age and duration of AED treatment are significant risk factors.[6-8]

In 1979, Offerman et al.[9] documented that 72% of 83 children aged 10 to 16 years with epilepsy and 50% of 16 control patients exhibited 25-hydroxy vitamin D (25OHD) <15 ng/mL. Since then, several cross-sectional

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studies evaluated the prevalence of hypovitaminosis D in pediatric epilepsy. Among children taking AEDs, nonambulatory children,[10] polytherapy,[5,10,11] and those with poorly nutritional status[12] were reported to have a high prevalence of vitamin D deficiency or insufficiency or significantly lower 25OHD levels. However, there are few studies that evaluate the longitudinal change of 25OHD levels among children with epilepsy on AEDs in accordance to diverse risk factors.

The aims of this study, therefore, were (1) to evaluate the prevalence of vitamin D deficiency or insufficiency among children with epilepsy on AED treatment (greater than 1 year); (2) to examine the longitudinal change of 25OHD levels during AED treatment; and (3) to evaluate the potential risk factors for hypovitaminosis D in a tertiary pediatric neurology clinic.

Patients and Methods

Patients

We undertook a retrospective longitudinal cohort study of children on AEDs between January 2011 and March 2013 at a pediatric neurology clinic affiliated with Pusan National University Children's Hospital in South Korea. The inclusion criteria of the study subjects were as follows: (1) the range of patients' age was between 1 and 18 years; (2) patients were monitored for at least 1 year after the start of AED treatment; and (3) their levels of serum 25OHD were measured before the start of AED treatment and at 6 to 12 months' interval thereafter. The exclusion criteria were as follows: (1) presence of any condition known to affect the bone metabolism (e.g., hepatic, renal, endocrine, and metabolic disease) and other chronic diseases (e.g., cancer, gastrointestinal disorders, liver insufficiency, diabetes mellitus); (2) intake of vitamin D and calcium supplements within the last 6 months; and (3) have taken drugs that may potentially affect the bone metabolism (e.g., corticosteroids).

Methods

The levels of serum 25OHD of all patients were measured before the start of AED treatment (25OHD-1; baseline 25OHD) and every 6 to 12 months' interval thereafter (25OHD-2; 25OHD measured at the last follow-up visit) by isotope-dilution liquid chromatography-tandem mass spectrometry in a licensed laboratory. Recent reviews have defined vitamin D deficiency as 25OHD $<$20 ng/mL and vitamin D insufficiency as between 21 and 29 ng/mL.[13-15] These definitions were used in our study. The difference or change between 25OHD-1 and 25OHD-2 (D-25OHD) was investigated as the value of 25OHD-2 minus 25OHD-1. We divided the patient population into two groups by the value of D-25OHD: (1) patients with unnoticeable decreased value (D-25OHD ≥ -10 ng/mL, group A) and (2) patients with significant decreased value (D-25OHD < -10 ng/mL, group B). Decline of more than 10 ng/mL from the baseline to the last follow-up was suggested as the longitudinally significant decreased value.

Potential risk factors for hypovitaminosis D were evaluated by comprehensively reviewing the patients' medical records, which included sex, age at the start of AED treatment, ambulatory status, feeding status (oral versus tubal), ketogenic diet, BMI (kg/m^2), underlying etiologies, seizure outcomes (seizure free versus no seizure free), number of regular AEDs over the last 6 months, and duration of AEDs ($<$2 years versus $\geq$2 years). Patients with monotherapy were classified as taking "enzyme-inducing" or "nonenzyme-inducing" AEDs. Enzyme-inducing AEDs included phenytoin, phenobarbital, and carbamazepine. Nonenzyme-inducing AEDs included vigabatrin, lamotrigine, levetiracetam, topiramate, clobazam, valproate, and ethosuximide. Seizure-free outcome was defined as no seizure for at least 1 year until the last follow-up. Etiologies were defined as magnetic resonance imaging (MRI) negative if no known etiology had been identified and brain MRI was normal. MRI positive was defined if there was a brain lesion present, such as previous acquired brain injuries or developmental brain malformations. BMI of greater than eighty-fifth percentile for their age was defined as being overweight.

TABLE 1.
Demographic Profile of the Patients

Variable	n (%)
Total	143 (100.0)
Sex	
Boy	103 (72.0)
Girl	40 (28.0)
Mean age ± SD (yr)	7.4 ± 5.4 (1.0-18.5)
Brain MRI	
No lesion	99 (69.2)
Lesion	44 (30.8)
AEDs	
Monotherapy	77 (53.8)
Non-EIAEDs	58 (40.6)
EIAEDs	19 (13.3)
Polytherapy	66 (46.2)
Duration of AEDs	
1-2 yr	91 (63.6)
$>$2 yr	52 (36.4)
Mean duration (yr)	1.8 ± 0.8 (1.0-4.9)
Seizure outcomes	
Seizure free	76 (53.1)
No seizure free	67 (46.9)
Nonambulatory	42 (29.4)
Tube feeding	20 (14.0)
Ketogenic diet	16 (11.2)
BMI (percentile for age)	
$<$85th	93 (65.0)
$\geq$85th	50 (35.0)
Mean BMI (kg/m^2)	18.2 ± 4.9 (8.2-36.5)

Abbreviations:
AEDs = Antiepileptic drugs
BMI = Body mass index
EIAEDs = Enzyme-inducing AEDs
MRI = Magnetic resonance imaging
SD = Standard deviation

Standard protocol approvals, registrations, and patient consents

Ethics permission for this study was granted (number: 05-2014-066) by the Institutional Review Board of Pusan National University Yangsan Hospital, and fully informed written consent was obtained from each participant.

Statistical analysis

Statistical analyses were performed with SPSS 15.0 software using raw scores. For the initial and/or last 25OHD (25OHD-1 versus 25OHD-2) comparison in all patients, a paired *t* test was used to evaluate the significant changes between the corresponding values (25OHD-2 minus 25OHD-1). Two-tailed chi-square and Student *t* tests were used to evaluate the significant differences in dependent, categorical, and continuous variables between groups. Multivariate logistic regression was used to identify the variables that were independently associated with longitudinally significant decrease of the 25OHD. Sex, age, ambulatory status, feeding status, ketogenic diet, BMI, underlying etiologies, seizure outcomes, and number, types, and duration of AEDs were all entered as independent variables. Statistical significance was determined as a two-tailed *P* value of $<$0.05.