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The impact of the use of antiepileptic drugs on the growth of children

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Abstract

Background: This study investigated whether long-term treatment with antiepileptic drugs (AEDs) had negative effects on statural growth and serum calcium levels in children with epilepsy in Taiwan.

Methods: Children with epilepsy treated with one prescription of AEDs (monotherapy) for at least 1 year were selected. The AEDs included valproic acid (VPA; Deparkin) in 27 children (11 boys and 16 girls) aged 4-18 years, oxcarbazepine (Trileptal) in 30 children (15 boys and 15 girls) aged 5-18 years, topiramate (Topamax) in 19 children (10 boys and 9 girls) aged 6-18 years, and lamotrigine (Lamicta) in eight children (5 boys and 3 girls) aged 5-13 years. Patients with a history of febrile convulsions were selected as the controls.

Results: One year of VPA treatment significantly impaired the statural growth of pediatric patients with epilepsy (p < 0.005) compared with the control group. The underlying mechanism may have been due to the direct effect of VPA on the proliferation of growth plate chondrocytes rather than alterations of serum calcium.

Conclusions: These results raise serious concerns about the growth of pediatric epilepsy patients who use AEDs, and potentially the need to closely monitor growth in children with epilepsy and adolescents under AED treatment, especially VPA.

Keywords: Antiepileptic drugs, Valproic acid, Oxcarbazepine, Topiramate, Lamotrigine

Background

The skeletal system determines a person’s height. Although stiff and unyielding, bone is a living tissue that continuously remodels throughout life. Specialized cells are engaged in the bone remodeling and turnover processes, such as osteoblasts initiating bone formation, osteocytes monitoring bone mechanical stresses, and osteoclasts absorbing bone [1]. The growth plate is at the end of long bones, is made up of chondrocytes at different stages of differentiation, and is divided histologically into three distinct zones: resting, proliferative, and hypertrophic [2]. Longitudinal bone growth is primarily achieved through the action of chondrocytes in the proliferative and proliferative zones of the growth plate [3]. Apart from the effects of circulating systemic and local hormones, calcium and other chemicals, which are mainly provided by bone to maintain the intra- and extracellular mineral pools, can work in cohort with osteoblasts, osteocytes, and extracellular matrix proteins to mineralize osteoid [4]. Calcium is crucial for normal epiphyseal growth plate development, and changes in extracellular calcium modulate the function of chondrocytes [5]. Proliferation of epiphyseal growth plates results from a complex interplay among a net effect of hormones and growth factors, which may directly or indirectly affect the serum levels of calcium and the condition of those cells, leading to final stature.

Epilepsy is a chronic condition characterized by recurrent clinical events or epileptic seizures, which occur in the absence of a metabolic or toxic disease or fever [6]. In addition, the diagnosis of epilepsy can possibly be made after only one epileptic seizure if an “endearing predisposition of the brain to future seizures” exists. The World Health Organization (2001) estimates a prevalence of 0.8% in the general population, and the prevalence in Taiwan has been reported to be 0.28% [7]. Epilepsy often requires long-term antiepileptic drug (AED) therapy. However, prolonged AED administration is associated with a number of problems such as behavioral and psychiatric...
disorders, metabolic and endocrine disorders, idiosyn- 
cratic reactions, and drug interaction effects [8]. Although 
some studies suggest that patients with epilepsy treated 
with AEDs have an increased risk of fractures, low bone 
mineral density (BMD), and abnormalities in bone meta-
bolism, skeletal diseases associated with long-term AED 
treatment are seriously unrecognized [9,10]. In a survey 
of >1000 adult and pediatric neurologists designed to 
assess the awareness of the effects of AED therapy on 
bone health, only 28% of adult and 41% of pediatric 
neurologists reported screening their patients for bone 
diseases [11]. A lack of consensus between physicians con-
cerning the impact of AED therapy on bone may put epi-
lepsy patients at risk, especially children, with regard to 
bone health or developing bone diseases.

Evidence suggests that patients with epilepsy are predis-
posed to bone problems and fractures [12]. However, one 
meta-analysis concluded that the deficit in bone mineral 
density was too small to explain the increase in the risk of 
fractures in patients with epilepsy [13]. Bone abnormalities 
such as short stature, abnormal dentition, rickets, and 
osteomalacia have been reported to be linked to the use of 
AEDs [12,14,15]. The mechanisms through which AEDs 
cause abnormal bone metabolism and increase fractures 
are not fully understood. Reports have shown that hypo-
calcemia is an important biochemical abnormality in pa-
tients receiving cytochrome P450 enzyme-inducing AEDs, 
which potentially increase the catabolism of vitamin D to 
inactive metabolites, leading to reduction of calcium 
[9,10,16]. However, some non-enzyme-reducing AEDs 
have also been linked with low bone mass [10,17,18]. A 
new generation of AEDs, including oxcarbazepine (OXA), 
topiramate (TPM), and lamotrigine (LTG), have been 
approved as therapeutic options for epilepsy. However, to 
date, there is no consensus about the effect on bone 
metabolism in individuals receiving these AEDs, and no 
definitive guidelines for evaluation or treatment have yet 
been determined. Most epileptic patients are diagnosed 
and treated in childhood and adolescence, and this period 
is crucial in attaining peak bone mass. Therefore, it is 
worth investigating whether AEDs affect bone growth in 
pediatric patients with epilepsy.

The maintenance of growth and bone health is a com-
plex process that can be influenced by the underlying 
diseases and nutritional status of a patient, but also by 
chemical factors. If AED treatment is associated with 
disturbance of statural growth and calcium metabolism, 
clinical parameters such as serum calcium levels and sta-
tural growth may reveal abnormalities after AED therapy 
in pediatric patients with epilepsy. The aim of this study 
was to evaluate the effects of AED monotherapy includ-
ing VPA, OXA, TPM, and LTG on alterations in serum 
calcium levels and statural growth in drug-naïve, Taiwanese 
pediatric patients newly diagnosed with epilepsy. To gain 
further insight into the mechanism of action of AEDs on 
linear bone growth, we examined the effects of AEDs on 
cultured growth plate chondrocytes in vitro on cell prolif-
eration using a tetrazolium methylthiotetrazole (MTT) 
assay. Our results showed that, instead of affecting serum 
calcium levels, VPA may interfere with the proliferation of 
growth plate chondrocytes in a direct manner and signifi-
cantly affect the statural growth of children with epilepsy. 
These results raise serious concerns about the growth of 
pediatric epilepsy patients who use AEDs, and potentially 
the need to closely monitor growth in epileptic children 
and adolescents under AED treatment, especially VPA.

Methods

Study subjects

From February 2009 to January 2011, children with newly 
diagnosed seizures, which were classified according to the 
report of the International League Against Epilepsy (ILAE) 
Commission on Classification and Terminology 2005 [19], 
including generalized, tonic-clonic (ICD-9-CM diagnosis 
code 345.10), absence (ICD-9-CM diagnosis code 345.0), 
myoclonic (ICD-9-CM diagnosis code 345.1), clonic (ICD-
9-CM diagnosis code 345.2), tonic (ICD-9-CM diagnosis 
code 345.1), atonic (ICD-9-CM diagnosis code 345.1), and 
nonconvulsive (ICD-9-CM diagnosis code 345.5) seizures. The 
children were attending the pediatric outpatient department, 
earthy department, or were admitted to the pediatric 
ward and started on standard recommended doses of val-
proic acid (VPA; Depakine solution; Sanofi Winthrop 
Industrie, Paris, France; starting dose 20 mg/kg/day, main-
tenance dose 20-40 mg/kg); OXA (Trileptal suspension 
form; Novartis, Rueil-Malmaison, France; starting dose 
5-10 mg/kg/day, maintenance dose 20-40 mg/kg); TPM 
(Topamax 100 mg tablets, Janssen-Cilag, Baar, Switzerland; 
starting dose 0.5-1 mg/kg/day, maintenance dose 3-9 
mg/kg); or LTG (Lamictal 50 mg tablets, GlaxoSmithKline, 
Zeist, Netherlands; starting dose 0.5 mg/kg/day, main-
tenance dose 5-15 mg/kg) for at least 1 year. All children 
were ambulatory and without any dietary restrictions. The 
serum levels of patients taking VPA were routinely moni-
tored, and the levels were within the therapeutic range 
(50-100 μg/mL). Patients were excluded if they had: (1) a 
history of taking AEDs or other medications that affect 
bone metabolism (e.g., steroids, diuretics, vitamin D, 
calcium supplements, bisphosphonates, or calcitonin); 
(2) any endocrine or medical disorders (e.g., hypothy-
roidism or renal diseases); (3) a history of nutritional de-
fiency; (4) limitations in ambulation or daily physical 
activity; (5) any progressive neurological disorders other 
than epilepsy; and (6) clinical/biochemical evidence of 
rickets or growth retardation. All of the children resided 
in Taipei, were ambulatory, had normal age-appropriate 
activity, and nutritionally adequate diets. Subjects with a 
history of simple febrile convulsions (ICD-9-CM diagnosis
code 780.31) were selected as the control group. Body height, weight, and body mass index (BMI) were recorded. All patients were followed up every 3-6 months at the pediatric outpatient department.

**Estimation of serum calcium**

Five-milliliter venous blood samples were collected from all patients for the measurement of serum total and ionized calcium levels. Cobas c501 (Roche Diagnostics, Mannheim, Germany) and NOVA CCX (NovaBiomedical, Waltman, MA, USA) were used for the measurement of serum total and ionized calcium levels, respectively.

**Consent and ethical approval**

The current study was approved by the scientific and ethics committees of Tri-Service General Hospital and National Defense Medical Centre, Taipei, Taiwan (TSGHIRB approval number 100-05-239). All parents, guardians, or legal representatives signed an informed consent form before participation in the study.

**Reagents**

Dulbecco’s Modified Eagle’s Medium/Nutrient Mixture F-12 HAM Medium (DMEM/F-12) were purchased from Gibco Life Technologies (Carlsbad, CA, USA). Dimethylsulfoxide (DMSO), fetal bovine serum (FBS), and MTT were purchased from Sigma (St. Louis, MO, USA). All other reagents were purchased from Sigma and were tissue culture grade. The drugs were obtained as described above. In the *in vitro* study, the choice of AED concentration was based on therapeutic plasma concentrations of the respective drug in the patients. The following concentrations were used: VPA, 415 μM (60 μg/mL); OXA, 30 μM (7 μg/mL); TPM, 30 μM (10 μg/mL); LTG, 20 μM (5 μg/mL) [20].

**Cell isolation**

Chondrocytes were isolated and cultured as described previously [21]. Male 3-week-old Sprague–Dawley rats (50-60 g each) were obtained from BioLASCO Taiwan (Taipei, Taiwan). All experiments were approved by the local institutional animal care and use committee, Tri-Service General Hospital and National Defense Medical centre, Taipei, Taiwan, ROC (IACUC-12-233). The epiphyseal growth plate of the tibia was separated by cleaving the cartilage plate of muscular tissue, periosteum, and perichondrium. The proximal epiphysis was divided by a transverse cut with a sharp scalpel, and the cartilage plate was separated distally from the calcification zone of the tibial metaphysis. Isolated growth plates were digested with 3 mg/mL collagenase type H (Sigma) for 3 h at 37°CC. After thorough washing, cells were counted using a Neubauer chamber. Cell viability, examined by trypan blue exclusion, was >95%.

**Monolayer cultures**

Cell monolayers were cultured in DMEM/F-12 medium supplemented with 10% FBS, 100 IU/mL penicillin (Gibco), and 100 mg/mL streptomycin (Gibco). The cells were grown in 75-cm² plastic culture flasks (Corning, Corning, New York, NY, USA) and incubated at 37°CC until confluence. They were then washed three times with phosphate-buffered saline (PBS), harvested using trypsin-EDTA (Gibco), and subcultured at a 1:3 ratio. Chondrocytes were immunopositive for anti-S100 protein (data not shown). Growth-plate chondrocytes grown to passages 3 and 5 were then plated at 1 × 10⁴ cells/mL into 96-well plates for the MTT assay. The medium with the AEDs was changed daily and cells were collected for assay on Day 5. All cells were maintained in an atmosphere of 5% CO₂ and 95% air at 37°CC.

**Evaluation of rat chondrocyte proliferation by a MTT assay**

Cell viability was determined by measuring the activity of cellular dehydrogenase that could cleave MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (Sigma) in a colorimetric assay as described previously [22]. Activate dehydrogenase reduced MTT in viable cells to form insoluble formazan, which was then dissolved in DMSO and quantified spectrophotometrically at 540 nm. Growth-plate chondrocytes (1 × 10⁴ cells/mL) were seeded into 96-well plates (Corning) in triplicate and kept under 5% CO₂ at 37°CC. After 24 h incubation, the cell culture medium was replaced daily by one containing fresh complete medium or fresh complete medium with 0.1% DMSO as a vehicle, or fresh complete medium with an AED for 5 days. Two hundred microliters of MTT (0.5 mg/mL) was then added to each well and the mixture was left to incubate for 3 h at 37°CC. The reaction was then stopped by injecting 200 μL DMSO per well. The plates were shaken for 5 min, and then the optical density at 540 nm was determined on a microplate reader (μQuant, BIO-TEK Instruments Inc., Winoski, VT, USA) with KC Junior analysis software, version 1.5 (BIO-TEK Instruments). At least three such experiments were performed for each treatment.

**Statistical analysis**

All statistical analyses were performed using SPSS software, version 13.0 (Chicago, IL, USA). Age, sex, weight, BMI, AED, and levels of calcium were expressed as the mean ± standard deviation (SD). Comparisons of the data were conducted by one-way analysis of variance (ANOVA). The Student’s paired *t* test was used to compare serial changes in serum calcium after 1-year treatment with AEDs and the control group. Comparisons of the data from cell proliferation studies were carried out by ANOVA. A *p* value <0.05 was considered statistically significant; *represents *p* < 0.05 and **p* < 0.005.
Results
Clinical characteristics
The demographic characteristics of the patients are shown in Table 1. There were no significant differences between the control and study patients in age, sex, height, weight, or BMI.

Changes in statural growth
A statistically significantly lower body height was found in patients treated with VPA compared with the controls \((p < 0.005; \text{Figure 1})\). However, there were no significant differences between the control group and patients treated with OXA, TPM, or LTG.

Serum total and ionized calcium levels
Levels of serum total and ionized calcium did not differ significantly among the patients treated with VPA, OXA, TPM, and LTG compared with the controls \((p > 0.05; \text{Figure 2})\). None of the drugs affected the level of serum calcium in the epilepsy patients.

Evaluation of growth-plate chondrocyte proliferation
The influence of the vehicle (0.1% DMSO) and AEDs, including VPA, OXA, LTG, or TPM on growth-plate chondrocyte proliferation was expressed as a percentage of cell growth in six independent experiments. In comparison with the controls, the cell proliferation rate was significantly decreased to \(84.45 \pm 2.3\%\) when the cells were exposed to VPA. However, there were no significant effects on the proliferation of the chondrocytes with OXA, LTG, or TPM (Figure 3).

Discussion
In the current study, there were significant reductions in statural growth in the epilepsy patients who were treated with VPA for 1 year compared with the control group. However, there were no significant differences in statural growth in those who were treated with OXA, LTG, or TPM. In support of our findings, Sheth et al. [23] and Kafali et al. [24] reported decreased bone mass in the lumbar spine and middle of the distal radius in children without physical handicaps who were treated with VPA for \(\geq 6\) [23] or 18 [24] months. This suggests that VPA can disturb bone growth. Childhood and adolescence are crucial periods in which to attain peak bone mass, and most patients with epilepsy are diagnosed and treated in this period, therefore, AEDs, and especially VPA, should be used with caution in pediatric patients with epilepsy.

Calcium is crucial for normal epiphyseal growth plate development. However, hypocalcemia is reported to affect 3–30% of patients with epilepsy treated with AEDs [25], and this has been postulated to explain AED-associated

![Figure 1](image) **Figure 1** VPA significantly affected growth of children with epilepsy. Comparison of changes in body height among the control group and children with epilepsy treated for 1 year with AEDs, including VPA, OXA, TPM, and LTG. The bars represent means, and the whiskers represent standard errors. Significant differences (**, \(p < 0.005\)) were found between the control group and the group with VPA treatment.

| Table 1 Clinical parameters of children with epilepsy |
|-----------------|--------|--------|--------|--------|--------|--------|
| VPA             | OXA   | TPM   | LTG   | Control |
| Subject number  | 27    | 30    | 19    | 8      | 30     |
| Age (mean ± SD) | 9.59 ± 3.90 | 10.43 ± 3.73 | 9.74 ± 3.28 | 7.50 ± 3.30 | 9.10 ± 4.22 | 0.36 |
| Gender (% Female) | 59% | 50% | 47% | 38% | 40% | 0.64 |
| Height (cm mean ± SD) | 129.76 ± 20.00 | 137.83 ± 20.49 | 133.79 ± 16.83 | 123.63 ± 16.95 | 133.77 ± 23.24 | 0.4 |
| Weight (kg mean ± SD) | 32.26 ± 17.47 | 37.06 ± 16.29 | 32.42 ± 14.25 | 26.81 ± 10.43 | 33.45 ± 16.60 | 0.54 |
| BMI (mean ± SD) | 18.05 ± 4.19 | 18.65 ± 3.94 | 17.28 ± 3.42 | 17.00 ± 3.09 | 17.59 ± 4.07 | 0.69 |

Age, sex, weight, height, and BMI in epilepsy patients before AED treatment and in the control group.
AEDs [27]. These results and others [28,29] support the notion that AEDs can cause bone loss without inducing hypocalcemia and vitamin D deficiency, suggesting that other mechanisms may be responsible.

VPA, a cytochrome P450 enzyme inhibitor, is widely used for the management of epilepsy [30]. In the current study, the statural growth of pediatric patients was significantly affected by the use of VPA compared with the control subjects, and this was not through alterations in the concentration of calcium. The reported effects of VPA on bone loss in patients with epilepsy are diverse, including accelerated or no bone loss [30-33], hyper- and hypocalcemia [33,34], or normal serum calcium level [35,36]. To clarify these contradictions, we examined the effects of AEDs on the proliferation of cultured growth plate chondrocytes in vitro, and showed that cell proliferation was significantly inhibited by VPA, which is similar to our clinical findings. However, also in agreement with our clinical findings, no distinct effects on the inhibition of proliferation in the growth-plate chondrocytes were seen in the patients who were treated with OXA, TPM, or LTG.

OXA, TPM, and LTG are approved for monotherapy or adjunctive therapy in patients with partial and generalized seizures. Despite being safer and having better tolerability, data regarding these new generation AEDs on bone health in children are controversial. OXA and TPM are cytochrome P450 isoenzyme inducers. Epilepsy patients treated with OXA are reported to have an increased risk of fractures [37], lower BMD [28], and decreased 25-hydroxyvitamin D3 levels [38]. TPM is associated with renal calculi, osteomalacia and/or osteoporosis [39], and mild hypocalcemia and increased bone turnover [40]. LTG does not induce or inhibit cytochrome P450 isoenzymes [41]. Children treated with LTG and/or VPA for >2 years have shorter stature, lower BMD, and reduced bone formation compared with controls [15]. However, because of combined therapy, the seizure status in those children may be more severe and their physical activity lower. A lower physical activity may cause more severe bone abnormalities than AEDs do. In fact, all available data indicate that LTG monotherapy does not alter BMD, calcium, or vitamin D levels [16,42,43]. Although we did not find disturbances in serum calcium and statural growth in the epilepsy patients who were treated with OXA, TPM, or LTG, our findings do not contradict previous reports. This is because OXA, TPM, and LTG may alter bone microstructure and bone turnover rate but maintain an adequate bone mass, leading to a normal statural growth rate in vivo and a normal proliferation of bone cells in vitro. Ultimately, all of these factors may have an impact on longitudinal skeletal growth and risk of fractures.

It was unclear how VPA directly interfered with the proliferation of growth-plate chondrocytes in the current study. VPA at a therapeutic dose is an effective inhibitor of

**Figure 2** AEDs did not affect the level of calcium in children with epilepsy. Comparison in the changes of serum total (A) and ionized (B) calcium concentration among the control group and children with epilepsy treated for 1 year with AED, including VPA, OXA, TPM, and LTG. The bars represent means, and the whiskers represent standard errors.

**Figure 3** VPA significantly reduced the proliferation of rat growth-plate chondrocytes. The influence of vehicle (0.1% DMSO) and AEDs, including VPA, OXA, LEV, LTG, and TPM on chondrocytes of rat growth-plate proliferation in MEM:HAM-F12 (1 : 1) medium with 10% FBS, expressed as cell growth percentages. The mean values are presented on top of the bars with the standard error value. (**, p < 0.005).
of histone deacetylases, producing hyperacetylation of histone tails and chromatin relaxation owing to disruption of histone–DNA and histone–histone interactions [44]. Apoptosis of chondrocytes is the main process for growth-plate remodeling, therefore, it is worth investigating whether VPA delays cell-cycle progression [45], modulates caspases and/or induces apoptosis [46], thereby causing inhibition of cell growth and proliferation, leading to short stature.

The current study had a number of limitations. First, the sample size was small and the duration of follow-up was only 1 year. It is possible that statistically significant lower statures would have been discovered after 1 year in children taking some or all of these AEDs if larger sample sizes and longer duration had been used. Second, the literature shows that enzyme-inducing AEDs increase the catabolism of vitamin D to inactive metabolites, potentially explaining why some enzyme-inducing AEDs are associated with increased risk of osteoporosis [9,14,15]. However, it has been reported that vitamin D deficiency may not affect BMD in epilepsy patients after correcting for age and duration on AEDs [27]. If the level of vitamin D is affected by AED, the downstream of the calcium level should be cascade. The lack of vitamin D was a limitation of our study for a more comprehensive understanding of AED on growth. Third, rat chondrocytes in the growth plate cannot truly represent in vivo human conditions. Finally, this study was not randomized. These limitations may have led to some bias in analyzing the effects of AED on the growth of children with epilepsy.

The use of these AEDs for children and adolescents with epilepsy is growing, and the number of reported side effects of the newer AEDs is increasing. Therefore, our findings are valuable, because we performed a longitudinal study on AED monotherapy that indicated the risks of short stature in pediatric patients receiving AEDs. Early identification and proper management of AED-related growth retardation and associated bone health require greater public awareness and understanding of these adverse effects in children and adolescents.

Conclusions
AEDs are effective and necessary for children with epilepsy. However, long-term AED therapy, and especially VPA, may predispose patients to growth and bone health abnormalities. Childhood and adolescence are crucial growth periods, thus, prevention of growth retardation and adverse bone health with the use of VPA may be addressed by judicious use of AEDs coupled with improved nutrition and promotion of weight-bearing activities. Moreover, the new generation of AEDs such as OXA, LTG, and TPM may be alternative choices because of fewer adverse effects.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
HS Lee, DM Salter, and HC Fan were involved in conception and design of the study and drafting the manuscript. HS Lee and DM Salter revised the manuscript critically for important intellectual content. SY Wang, CC Wang, SJ Chen, and HC Fan made substantial contributions to acquisition, analysis, and interpretation of data. All authors read and approved the final manuscript.

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