Bone Health and Antiepileptic Drugs in Children with Epilepsy: A Pilot Study

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ABSTRACT
Epilepsy, a chronic neurological disorder necessitating prolonged antiepileptic medication, has been associated with deficiencies in vitamin D and related bone disorders in children. This study aims to investigate the prevalence of vitamin D deficiency, calcium deficiency, and bone diseases in children undergoing antiepileptic drug (AED) therapy. A retrospective study was conducted on 60 children (0-16 years old) with epilepsy at King Fahad Specialist Hospital-Dammam from 2016 to 2018. Participants were administered 800 IU/day of vitamin D for 6 months. Comprehensive assessments, including tests for calcium, phosphorus, 25-hydroxyvitamin D (25-OHD), 1,25-hydroxyvitamin D (1,25 OHD), parathyroid hormone (PTH), thyroid function [thyroid-stimulating hormone (TSH)], alkaline phosphatase (ALP), and bone density, were performed after 6 months of oral vitamin D supplementation. No significant associations were observed between age, sex, age of onset, duration of epilepsy, symptoms of vitamin D deficiency, dietary factors, and the levels of calcium, phosphorus, 25-OHD, 1,25-OHD, PTH, TSH, ALP, and bone scan. Carbamazepine (CBZ) was the only AED that affected bone metabolism in general (P = 0.024). Calcium was mostly found to be abnormal after using AED with vitamin D (800 IU/day) for 6 months (P = 0.05). 25-OHD deficiency was associated with use of CBZ in pediatric epilepsy. Considering its potential impact on bone metabolism, higher vitamin D doses may be advisable for children on long-term AED therapy to mitigate these abnormalities.

KEYWORDS
epilepsy, antiepileptic drugs, vitamin D deficiency, bone diseases, pediatric epilepsy

INTRODUCTION
Epilepsy is the most common neurological disorder affecting approximately 50 million people worldwide in all age groups, which corresponds to 0.5% of the global burden of all diseases in developing countries (Reynolds, 2000). The pathophysiology of epilepsy is still not very well understood (Stafstrom and Carmant, 2015). Evidently, the concept of seizure is an imbalance or distortion between excitation and inhibition in the brain (Stafstrom, 2010) which can be due to genetic or acquired causes (Stafstrom and Carmant, 2015). Interestingly, seizures occurring in the developing brain are less likely to cause structural damage when compared to the adult brain (Moshé, 1993). Many patients are noted to have psychological consequences due to the seizures themselves or the accompanied therapy (Sirven, 2015). Unfortunately, despite the wide range of therapeutic response, some patients continue to suffer the consequences of uncontrolled epilepsy, for example, psychosocial stigma and death (Sirven, 2015). Epileptic drugs have been known to cause many side effects, including aggression, irritability, and agitation (Brodie et al., 2016). Onset during childhood is prevalent, with frequency rates ranging from 2.0 to 22.2 per 1000 children (International League Against Epilepsy, n.d.; Fisher et al., 2005). The persistence of epilepsy from childhood carries long-term challenges, emphasizing the need for a nuanced understanding of the disorder’s impact and the imperative to address both its immediate and enduring consequences.

Patients with epilepsy often require long-term administration of antiepileptic drugs (AEDs), exposing them to significant metabolic effects on bone health (Lazzari et al., 2013). Initially, attention was predominantly directed toward enzyme-inducing AEDs, known to stimulate cytochrome P450, thereby increasing vitamin D metabolism. However, emerging evidence suggests that the mechanisms underlying bone loss due to AEDs are multifaceted, with all categories of AEDs potentially contributing. These mechanisms encompass impaired calcium absorption, direct impact on bone cells, inhibition of calcitomin, and resistance to parathyroid hormone (PTH) ( Fitzpatrick, 2004). Notably, enzyme-inducing AEDs, due to their association with
reduced bone mineral density (BMD) and heightened fracture risk, have garnered particular attention. The pathophysiology of these adverse effects is linked to the influence of AEDs on vitamin D metabolism (Lee et al., 2010; Nakken and Taubøll, 2010). Inducing hepatic enzymes appears to increase the metabolism of 25-hydroxyvitamin D (25-OHD) to inactive metabolites, which, in turn, results in metabolic bone disease and hypocalcemia (Pack et al., 2004; Sheth, 2004; Lee et al., 2012). It is vital to have the necessary knowledge and understanding of the possible metabolic derangements associated with AED use as most of the bone effects remain subclinical for a substantial amount of time prior to manifesting clinically (Pack, 2003; Pack et al., 2005; Krishnamoorthy et al., 2009). Understanding these mechanisms is crucial for developing effective strategies to mitigate the impact of AEDs on bone health in patients with epilepsy (Pack, 2003; Pack et al., 2005; Krishnamoorthy et al., 2009).

In addition, the effects of AEDs on bone metabolism and the endocrine system are yet to be fully elucidated (Meier and Kraenzlin, 2011; Tolou-Ghamari, 2013; Tolou-Ghamari et al., 2013a,b; Suljic et al., 2018). Therefore, the aim of our present study was to investigate the effect of AEDs on vitamin D, calcium, phosphorus, 25-OHD, 1,25-hydroxyvitamin D (1,25-OHD), PTH, thyroid function test [thyroid-stimulating hormone (TSH)], alkaline phosphatase (ALP), and bone density after administering vitamin D (800 IU/day) for 6 months in pediatric epilepsy patients who were on AEDs.

SUBJECTS AND METHODS

Participants

The retrospective study involved 60 pediatric patients aged 0–16 years, consisting of 27 females and 33 males. The data were obtained from King Fahad Specialist Hospital-Dammam (KFSH-D). A senior neurologist conducted a comprehensive medical history review, assessed the type of AEDs administered, and performed physical and neurological examinations.

Inclusion and exclusion criteria of case controls

Patients with a history of at least two epilepsy seizures, occurring at least 24 h apart, and who were undergoing neurotherapy with AEDs for a minimum of 6 months were included. We excluded all participants who were on two or more AEDs, taking vitamin D supplements, or suffering from other systemic diseases or other neurological deficits.

All participants received a daily dose of 800 IU of vitamin D for a period of 6 months. The study comprehensively evaluated various parameters, including calcium (Ca), phosphorus (P), 25-OHD, 1,25-OHD, PTH, thyroid function test (TSH), ALP, and bone density. Initial assessments were conducted before the commencement of the vitamin D course, with subsequent measurements repeated 6 months post-treatment.

The retrospective analysis relied on available medical records to assess baseline levels of Ca, P, 25-OHD, 1, 25-OHD, PTH, TSH, ALP, and bone density, offering valuable insights into the impact of vitamin D supplementation on these parameters throughout the study’s duration.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 software. Mean and standard deviation were estimated for various variables. Descriptive statistics were used to describe the categorical and quantitative variables, whereas appropriate statistical tests were used to perform the univariate analysis. Univariate analysis was conducted using suitable statistical tests to examine individual variables. Analysis of variance (ANOVA) was utilized to compare continuous variables among different subgroups. The impact of each AED was evaluated through coefficients of correlation. A significance level of $P < 0.05$ was applied, signifying statistical significance. This comprehensive approach facilitated a detailed exploration of the data, providing insights into the relationships between variables and the influence of AEDs on various parameters in the pediatric epilepsy population.

This study was conducted at the Department of Pediatric Neurology, Neuroscience Center, KFSH-D. Approval was obtained from the Institutional Research Committee and Ethical Committee. The study was carried out in accordance with the code of international and local ethics (Declaration of Helsinki). This study was reviewed and approved by the local ethics committee of KFSH-D. Informed consent was obtained from all subjects.

RESULTS

In our study involving 60 patients (55% males, 45% females), aged 3 months to 16 years, with epilepsy duration ranging from 1 to 4 years (mean of 28.7 months), several notable findings emerged.

Carbamazepine impact

Carbamazepine (CBZ) was the sole AED demonstrating a significant effect on bone metabolism in general ($P = 0.024$), highlighting its distinctive impact among the studied AEDs.

Calcium abnormalities

Calcium levels were significantly affected after 6 months of AED use with vitamin D supplementation at a dose of 800 IU/day ($P = 0.05$), indicating a noteworthy impact on this mineral (Fig. 1).

Age, sex, and duration of epilepsy

No significant relationships were observed between age, sex, age of onset, duration of epilepsy, symptoms of vitamin D deficiency, diet, and various measured parameters, including
calcium, phosphorus, 25-OHD, 1,25-OHD, PTH, TSH, ALP, and bone scan.

**Comparison of other AEDs**

ANOVA did not reveal a significant effect on bone metabolism ($P = 0.05$) for other drugs, including phenobarbital, topiramate (TPM), valproate (VPA), lamotrigine (LTG), levetiracetam (LEV), gabapentin, and pregabalin (PGB).

**Specific effects of TPM and PGB**

When assessing the effects of various AEDs on specific parameters after administering vitamin D at a dose of 800 IU/day for 6 months, TPM and PGB demonstrated significant effects. TPM and PGB mainly affected calcium and phosphorus ($P = 0.028$ and $0.007$ in TPM, and $P = 0.018$ and $0.015$ in PGB, respectively). Additionally, PGB affected ALP ($P = 0.004$). These specific impacts indicate the importance of considering the unique effects of each AED on bone health when managing pediatric epilepsy patients.

**DISCUSSION**

AEDs play a pivotal role in managing epilepsy across diverse age groups, often involving extended treatment periods with substantial doses or combinations of drugs. However, the potential adverse effects of AEDs, particularly on bone and mineral metabolism, necessitate meticulous consideration throughout treatment (Pack, 2003; Nakken, 2011; Atmasari et al., 2017). Our study specifically examined the most commonly utilized AEDs in pediatric epilepsy, including CBZ, phenobarbital, sodium valproate, TPM, clonazepam, clobazam, and LTG.

Our findings underscored that among these AEDs, CBZ singularly affected bone metabolism significantly. This corresponds with existing research, reinforcing the fact that CBZ distinctly affects bone health (Suljic et al., 2018; Feldkamp et al., 2000). A meta-analysis by Zhang et al. (2020) discovered lower levels of vitamin D and calcium in patients using CBZ, consistent with our study’s outcomes. Nevertheless, the literature presents conflicting evidence regarding the association between CBZ and alterations in bone mineral metabolism and hypovitaminosis D.

Several studies have reported a connection between CBZ use and hypovitaminosis D (Rajantie et al., 1984; Nicolaidou et al., 2006; Tekgul et al., 2006; Kim et al., 2007; Misra et al., 2010). Conversely, other studies have highlighted uncertainties regarding the impact of CBZ on bone mineral metabolism, potentially leading to conditions such as osteopenia, osteoporosis, and increased fracture risks (Tjellesen et al., 1983; Ala-Houhala et al., 1986; Verrotti et al., 2002; Babayigit et al., 2006; Misra et al., 2010). Specifically, Chaudhuri et al. (2017) linked 25-OHD deficiency in pediatric epilepsy to the use of CBZ and sodium valproate. Furthermore, the extensive study by Suljic et al. revealed notably lower average vitamin D levels in serum among CBZ users compared to a control group (Suljic et al., 2018). These contrasting findings emphasize the complexity of the relationship between CBZ and bone health, underscoring the imperative for further research to elucidate the underlying mechanisms and clarify potential risks associated with its use.
Moreover, Vestergaard (2005) investigated the impact of AEDs on bone health and growth in children with epilepsy. VPA and CBZ exhibited a limited decrease in BMD when used as monotherapy, while oxcarbazepine, LEV, phenytoin, phenobarbital, and TPM showed no such decrease (Vestergaard, 2005). However, polytherapy was associated with a more significant reduction in BMD (Vestergaard, 2005). Although our findings indicate that sodium valproate has no effect on epileptic patients, Lee et al. observed that a year of VPA use significantly impaired the statural growth of pediatric epileptic patients, possibly due to VPA’s direct impact on the proliferation of growth plate chondrocytes (Lee et al., 2013). Guo et al. (2001) also concluded that long-term therapy with VPA and/or LTG is linked to short stature and a decrease in mineral bone density. However, they noted that these results might be attributed to decreased activity rather than the drugs themselves (Guo et al., 2001). Min et al. (2020) observed a significant decrease in BMD and 25-OHD with VPA use.

TPM and PGB significantly affected calcium and phosphorus, while PGB also influenced ALP. Neurontin significantly affected ALP. Therefore, careful attention must be paid to the adverse effects of AEDs to optimize treatment outcomes. It is evident that AEDs increase bone turnover, potentially contributing to bone loss (Ali et al., 2004; Pack et al., 2004; Valsamis et al., 2006). Hamed (2016) recommends the use of prophylactic calcium and vitamin D with continuous monitoring of bone health for all patients. In a study by Lazzari et al. (2013), comparing prophylactic vitamin D and calcium alone with the addition of risedronate, both groups showed increased BMD. However, the addition of risedronate proved effective in preventing vertebral fractures among male veterans with epilepsy compared to vitamin D and calcium alone (Lazzari et al., 2013). Teagarden et al. (2014) concluded that vitamin D deficiency was evident in 54% and 37% of adult patients on enzyme-inducing and non-enzyme-inducing AEDs, respectively. Therefore, supplementation with vitamin D and calcium could potentially help alleviate the side effects of AEDs on vitamin D metabolism in addition to optimizing seizure therapy.

Enzyme-inducing and non-enzyme-inducing AEDs often exhibit distinct effects on various physiological processes, including bone metabolism. Enzyme-inducing AEDs, such as CBZ, phenytoin, and phenobarbital, are known to stimulate hepatic enzymes, particularly cytochrome P450, leading to increased metabolism of vitamin D. On the other hand, non-enzyme-inducing AEDs, like valproic acid, LTG, and LEV, typically do not have a significant impact on hepatic enzymes.

**CONCLUSION**

The study findings indicate that calcium levels were observed to be abnormal after 6 months of vitamin D supplementation in patients. The recommendation emphasizes the importance of continuous monitoring to prevent the occurrence of abnormalities. Additionally, the use of vitamin D supplements was noted to help reduce the side effects of AEDs, suggesting that incorporating such supplements into the treatment regimen optimizes epileptic therapy for patients.

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**AUTHOR CONTRIBUTIONS**

RSA designed the study. RSA, NA, and SB collected the data and drafted the manuscript. All authors read and approved the final manuscript.

**COMPETING INTERESTS**

The authors declare that they have no competing interests.

**DATA AVAILABILITY STATEMENT**

The data are available on request from the corresponding author.
REFERENCES


