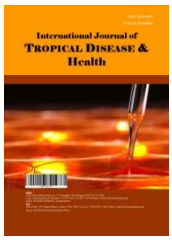

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Serum Calcium, Vitamin D3 and Bone Specific Alkaline Phosphatase Levels in Nigerian Children Treated with Antiepileptic Drugs: A Comparative Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aim of the Study: Studies have shown that serum 25-hydroxycholecalciferol, calcium and bone-specific alkaline phosphatase (B-ALP) are altered in children on antiepileptic drugs (AEDs), and these could result in poor bone mineralization. The study aimed to determine the serum 25-hydroxycholecalciferol, calcium, and B-ALP levels among children on AEDs attending the paediatric neurology clinic of the University of Port Harcourt Teaching Hospital (UPTH).
Methods: This cross-sectional analytical study was carried out from January 2018 to April 2019 on 100 children on AEDs and 100 age- and gender-matched healthy controls, aged 1.5 - 17 years. Data on socio-demography, AED regimen, and clinical examination findings of the subjects, their serum 25-hydroxycholecalciferol, calcium, and B-ALP levels were obtained and entered into a proforma. Data obtained were analysed using IBM SPSS version 20. Statistical significance was set at p-value of < 0.05.

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Results: The subjects had significantly lower mean serum 25-hydroxycholecalciferol and calcium and higher mean serum B-ALP levels than the controls, respectively. The mean serum 25-hydroxycholecalciferol was significantly lower in children on AED polytherapy. There was negative correlation between the duration of drug therapy and all serum biochemical indices but this was only significant for serum 25-hydroxycholecalciferol level (p = 0.027). Age significantly impacted negatively on serum 25-hydroxycholecalciferol, p = 0.036 and calcium levels, p = 0.009, but not on B-ALP (p = 0.392).

Conclusion: Children on antiepileptic drugs in UPTH had lower mean serum 25-hydroxycholecalciferol and calcium levels but higher mean serum BALP level than healthy controls, as well as inverse relationship between duration of AED therapy and 25, hydroxycholecalciferol, calcium and B-ALP. We therefore recommend children with epilepsy on antiepileptic drugs have their serum 25-hydroxycholecalciferol, calcium and B-ALP levels monitored to enable early detection of any abnormalities.

Keywords: Antiepileptic drug; epilepsy; Vitamin D; bone alkaline phosphatase; calcium; children; Nigeria.

1. INTRODUCTION

Epilepsy, according to the International League Against Epilepsy (ILAE), is a disease of the brain defined by any of the following: at least two unprovoked seizures occurring more than 24 hours apart; or one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (more than 60%) after two unprovoked seizures, occurring over the next ten years; or a diagnosis of an epilepsy syndrome [1,2]. The prevalence in African countries ranges from 5.2 to 58 per 1000 [3] while in Nigeria, it ranges from 5.7 to 37 per 1000 [4]. Studies done in several Paediatric Neurology clinics across Nigeria have shown that epilepsy accounts for 24.6 to 60% of all neurological cases [5–11].

Most cases of epilepsy can easily be treated with relatively inexpensive antiepileptic drugs [12]. The readily available antiepileptic drugs include Phenobarbitone, Carbamazepine, Sodium Valproate, and Phenytoin. These among others are listed in the World Health Organization Essential Drug List for children [13] and the Essential Medicine List of the Federal Republic of Nigeria [14]. These drugs are usually taken by the patients for long periods, with a recommendation that the patient has been seizure-free for at least two years before the drugs, are slowly discontinued [3]. Alteration in Vitamin D and calcium metabolism is one of the metabolic and endocrine side effects of the antiepileptic drugs, which subsequently affects bone mineral metabolism. Vitamin D is a regulator of calcium and phosphate homeostasis, as well as bone formation and maintenance.

Some of the AED such as Phenobarbitone, Carbamazepine, and Phenytoin induce hepatic cytochrome P450 enzymes causing an increased breakdown of 25-hydroxycholecalciferol into inactive metabolites which include 24,25 dihydroxycholecalciferol and 3,25 dihydroxycholecalciferol, [15]. while, Sodium Valproate is thought to be toxic to the chondrocytes and osteoblasts required for bone formation [16, 17]. These effects on bone often remain subclinical for long periods and only manifest clinically after many years [18]. This is important in children as childhood is the critical period for skeletal development [19] and peak bone mineral density (BMD) is attained between the second and third decades of life [20]. Alkaline phosphatase and its isoenzyme, bone alkaline phosphatase (B-ALP) are markers for osteoblasts activities and their cellular levels correlate with rates of bone formation and / or destruction. B-ALP is reported to be increased in children receiving carbamazepine and sodium valproate, [21] leading to increasing bone turn over and increases the risk of osteoporosis and fractures. AEDs have also been reported to reduce bone density, growth velocity leading to short stature later in life [22-25]. Factors identified as possible risk factors for lower 25-hydroxycholecalciferol levels in children on AED include drug polytherapy, duration of therapy, generalized seizures, and use of enzyme-inducing antiepileptic drugs [26-28]. In Nigeria there have been limited studies on this subject and the deficiencies of 25-hydroxycholecalciferol and bone-specific markers such as bone-specific alkaline phosphatase have not been evaluated in children with epilepsy.

This study aimed to determine if these biochemical abnormalities (low 25-hydroxycholecalciferol, hypocalcemia, and increased B-ALP levels) were present in children

on antiepileptic drugs in the University of Port Harcourt Teaching Hospital and also determine if there are possible risk factors associated with these abnormalities in these children.

2. METHODS

This cross-sectional analytical study involved children with epilepsy on antiepileptic drugs and age and gender-matched healthy pupils of the University of Port Harcourt Staff School, who were not on antiepileptic drugs, over a 16-month period (January 2018 to April 2019).

The Paediatric Neurology clinic runs every Friday from 8 am to 4 pm and attends to children with various neurological disorders which include epilepsy, neurodevelopmental delays, and neuro-behavioural disorders such as autism, and attention deficit hyperactivity disorder (ADHD). As of January 2018, 130 children were on follow-up for epilepsy in the clinic, with an average of 10 being seen per week in the clinic.

A sample size of 100 children on antiepileptic drugs and 100 gender and age-matched children was calculated using the formula:

$$n = \frac{(u+v)^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

All children on antiepileptic drugs (carbamazepine, sodium valproate, phenobarbitone, and levetiracetam), who met the selection criteria were consecutively recruited until the sample size was attained. Informed consent and assent, for children aged seven years and above, were obtained. Age and gender-matched children who were not on antiepileptic drugs were recruited from the University of Port Harcourt Staff Primary and Secondary Schools after obtaining informed consent and assent. Their ages were matched against the subjects on antiepileptic drugs to the nearest three months; e.g. a 5-year-old (60 months old) subject on an antiepileptic drug, was matched against a healthy subject who was aged 5 years ± 3 months.

2.1 Study Procedure

A chemical pathology laboratory scientist in the UPTH research laboratory, in collaboration with the authors, analysed the serum obtained for calcium, bone-specific alkaline phosphatase, and 25-hydroxycholecalciferol levels.

For each recruited subject, five millilitres of venous blood were collected from a prominent or large bore vein without a tourniquet, into a plain bottle and kept in an icebox at - 4^0 C. The samples were then sent to the laboratory on the day of collection and centrifuged to obtain serum on the same day. The serum samples were decanted into universal plain bottles and stored in the refrigerator at -20^0 C until they were analysed for serum bone-specific alkaline phosphatase, calcium, and 25-hydroxycholecalciferol.

On the day of analysis, the stored serum samples were brought to room temperature (25 – 28^0 C) by allowing them to thaw for two hours before the estimation of the serum 25-hydroxycholecalciferol, calcium, and B-ALP. Ten microliters (10µL) of the 25-hydroxycholecalciferol standards, controls, and samples were added into each well. Then two hundred microliters (200µL) of working solution of Biotinylated 25-hydroxycholecalciferol reagent were added into each well. The contents of the well were carefully mixed for twenty seconds using a plate shaker at 200 revolutions per minute (RPM). The plate was removed from the shaker and covered with the adhesive plate seal. The serum 25-hydroxycholecalciferol was analysed using an enzyme-linked immunosorbent assay (ELISA) kit with catalogue number: VD220B® by CALBIOTECH, El Cajon, California, USA. Serum calcium was determined using the o-Cresolphthalein colorimetry kit with batch number BXCO291A produced by Fortress Diagnostics Limited®, Antrim, Northern Ireland, United Kingdom. The assay was able to measure the serum calcium in a range of 0.58 - 5.5mmol/l and had a detection limit of 0.12mmol/l (0.5mg/dl).

The serum B-ALP activity was determined by enzyme-linked immunoassay (ELISA), using the Human B-ALP ELISA kit with batch number E-EL-H0584 by Elabscience Laboratories®, Houston, Texas, USA. The results determined were expressed as micrograms per litre (µg/l). The assay was able to measure the serum B-ALP levels in the range of 2 to 140 µg/l. The normal reference range for calcium is 2.2 - 2.6mmol/l.

2.2 Operational Definitions

Serum calcium level less than 2.2 mmol/l was taken as hypocalcaemia. Serum 25-hydroxycholecalciferol level, less than 20ng/ml, were considered as 25-hydroxycholecalciferol deficiency, whereas levels of 20-29.9ng/ml were

taken as insufficient, 30-100ng/ml sufficient, and greater than 150ng/ml as intoxication. The reference range for B-ALP varies with age and sex. In males aged less than 2 years is 25 - 221µg/l; for 2 - 9 years is 27 - 148 µg/l; for 10 - 13 years is 35 - 169 µg/l, and for 14 - 17 years is 13 - 111µg/l. While in females, the range is as follows; those aged less than 2 years 28 - 187µg/l; 2 - 9 years 31 - 152 µg/l; 10 - 13 years 29 - 177µg/l; and 14 - 17 years 7 - 41 µg/l.

2.3 Data Processing and Analysis

Data obtained were all entered into an excel sheet and analysed using IBM Statistical Package for the Social Sciences (SPSS) version 20.0 software. The independent t-test was used to compare the differences in the means of the serum 25-hydroxycholecalciferol, calcium, and B-ALP levels between the two groups of children, sexes of children with epilepsy and the type and number of AED being taken. Pearson's correlation was used to test the relationship between the serum 25-hydroxycholecalciferol, calcium, and B-ALP levels and the age of children on AED and duration of AED therapy. Multiple linear regression was used to predict relationship the serum 25-OH vitamin D_3 levels and multiple independent variables (age, number of AED taken, and duration of AED). Statistical significance at a 95% confidence interval was set at a p-value <0.05.

3. RESULTS

3.1 Socio-Demographic Characteristics and Biochemical Parameters of the Study Subjects

One hundred and ten children on AED met the inclusion criteria. Ten subjects were excluded because of the spillage of samples in the laboratory, therefore data from 100 children on AED and 100 age and gender-matched healthy controls were analysed. The subjects' ages ranged from 1.5 - 17 years, with mean of 7.68 ± 4.47 years while that of controls was 7.71 ± 4.49 years, t = -0.047, p = 0.962. There were 69 males and 31 females in each group, with a male to female ratio of 2.2:1. A high proportion (60%) of the study population were in the high socio-economic class. The prevalence of subnormal 25-hydroxycholecalciferol levels (insufficient and deficient levels) was higher in subjects on AEDs (22%) than in the controls (11%), p = 0.05. While 5% of subjects on AEDs had 25-hydroxycholecalciferol deficiency, none of the controls had deficient levels. Hypocalcemia was seen in 62% of cases as against 27% amongst the controls (p = 0.0001). Also elevated B-ALP levels were significantly more in the subjects on antiepileptic drugs, p = 0.020 Table 1.

The mean levels of 25-hydroxycholecalciferol and calcium were significantly lower in the subjects than in the controls (p<0.01 and <0.001 respectively). The serum mean B-ALP level was significantly higher among the subjects on AED than the AED-free subjects (p<0.001) Table 2.

Though only 7 subjects were on polytherapy, their mean serum 25-hydroxycholecalciferol was significantly lower than those on monotherapy, Table 3.

The multiple linear regression analysis, as shown in Table 4, indicated that the duration of antiepileptic drug therapy, number of AED, and the age of the children on antiepileptic drugs, explained 8.6% of the variance in serum levels of 25-hydroxycholecalciferol in children on antiepileptic drugs. The model was a significant predictor of the serum levels of 25-hydroxycholecalciferol in the subjects, (F = 2.995, p = 0.035) The duration of AED therapy was the only factor among the three found to significantly predict the serum 25-hydroxycholecalciferol levels in these children (β = -0.224, p = 0.027).

4. DISCUSSION

This study demonstrated a significantly lower mean serum 25-hydroxycholecalciferol level in children on AED in comparison with healthy controls. A similar finding had been described in previous studies in 2013 in Egypt by Elnady et al, [26] and in 2015 in India by Chaudhuri et al. [29] These two earlier studies were done with children of similar age range who were mostly on the same AED (Carbamazepine, Sodium Valproate, Phenobarbitone) as the children in the current study and both studies were done in the tropics (which have long hours of sunlight). However, Ramelli et al in a 2014 report noted no significant difference between the mean serum 25-hydroxycholecalciferol levels of Swiss subjects on AED and those that were not on antiepileptic drugs [30]. The subjects in this Swiss study were predominantly on non-enzyme-inducing AED such as Ethosuximide, Lamotrigine, Levetiracetam, Topiramate, Valproate, and Vigabatrin. The significantly lower mean serum 25-hydroxycholecalciferol level in

Table 1. Socio-demographic and biochemical characteristics of study subjects

Variables	Subjects (100) n (%)	Controls (100) n (%)	Total (200) n (%)	χ^2/Fishers exact	p-value
Age (years)					
1-5	36 (36.0)	36 (36.0)	72 (36.0)		
6–10	37 (37.0)	37 (37.0)	74 (37.0)	0.000	1.000
11–15	21 (21.0)	21 (21.0)	21 (21.0)		
≥16	6 (10.0)	6 (10.0)	12 (6.0)		
Serum 25-hydroxycholecalciferol (ng/ml)					
Deficient (< 20.00)	5 (5.0)	0 (0.0)	5 (2.5)	7.508	0.05
Insufficient (20.00–29.99)	17 (17.0)	11 (11.0)	28 (14.0)		
Normal (30.00 – 100.00)	75 (75.0)	83 (83.0)	158 (79.0)		
High (>100.00)	3 (3.0)	6 (6.0)	9 (4.5)		
Serum Calcium					
Deficient (≤ 2.1 mmol/l)	62 (62.0)	27 (27.0)	89 (44.5)	23.582	0.0001*
Normal (2.2 – 2.6 mmol/l)	38 (38.0)	73 (73.0)	111 (55.5)		
Serum B-ALP					
Elevated	15 (15.0)	4 (4.0)	19 (9.5)	7.809	0.020*
Normal	85 (85.0)	96 (96.0)	191 (90.5)		

**Statistically significant*

Table 2. Mean serum levels of 25-hydroxycholecalciferol, calcium and B-ALP of subjects.

Serum Biochemical Parameter	Study groups			
	Subjects (n=100) Mean ± SD	Controls (n=100) Mean ± SD	t-test	p-value
Serum 25-hydroxycholecalciferol (ng/ml)	46.53 ± 24.46	56.55±30.43	-2.569	0.011*
Serum calcium (mmol/l)	2.09 ± 0.16	2.27±0.15	-7.570	0.0001*
Serum B-ALP (µg/l)	84.85±52.54	56.83±26.94	4.741	0.0001*

**Statistically significant*

Table 3. Comparing mean serum levels of 25-Hydroxycholecalciferol, Calcium, and B-ALP with number of antiepileptic drugs

	AED Number Category			
	Monotherapy (n=93)	Polytherapy (n=7)		
Biochemical parameter	**Mean ± SD**	**Mean ± SD**	**t-test**	**p-value**
Serum 25-hydroxycholecalciferol (ng/ml)	47.85±24.84	29.00±5.15	1.995	<0.05*
Serum calcium (mmol/l)	2.11±0.16	2.00±0.20	1.648	0.102
Serum B-ALP (µg/l)	87.00±53.80	56.43±14.23	1.493	0.139

**Statistically significant*

Table 4. Multiple linear regression of predictors of serum 25-hydroxycholecalciferol levels in children on antiepileptic drugs

Factors		**Unstandardized Coefficients**		**Standardized Coefficients**	**T**	**p-value**
		B	**Std. Error**	**B**		
1	Constant	69.397	11.275		6.147	0.000
	Duration (years)	-1.924	.988	-0.224	-2.238	0.027*
	AED number	-12.569	10.356	-0.125	-1.144	0.225
	Ages (years)	-0.890	.557	-0.157	-1.548	0.125

*R^2 = 0.086; F = 2.995; df = 3; p = 0.035; *Statistically significant*

the subjects in the present study shows that children on AED are at a risk of reduced 25-hydroxycholecalciferol with the attendant risk to bone health. Therefore, these children would require regular monitoring of their 25-hydroxycholecalciferol levels and early intervention with Vitamin D supplementation, if the levels are deranged. They should also be encouraged to have diets rich in Vitamin D containing foods such as fish, eggs, fish oils, vegetable oils, palm oil, margarine, beef liver, fortified milk, and seafood such as shrimps and to have more outdoor activities to increase their sunlight exposure.

In this study, 5 % of subjects had 25-hydroxycholecalciferol deficiency which is significantly lower than that of an earlier report in 2008 by Nettekoven et al in Germany; 76% in subjects on AED and 23% in healthy children [31]. The huge difference between both studies may have been due to the varying amount of sunshine between Hanover, Germany with a temperate climate and Port Harcourt, with a tropical climate. Furthermore, two-thirds of the samples in the German study were collected during spring and winter when the amount of sunshine is much lower, and the cold weather would limit outdoor activity, invariably leading to much lower serum 25-hydroxycholecalciferol levels. The small sample size of 38 in the German study, in comparison with 100 in the present study, may have also contributed to the difference in the prevalence of 25-hydroxycholecalciferol deficiency in the two studies. In addition, more than two-thirds of the subjects on AED in the German study were on polytherapy compared to seven percent in the present study, contributing to the high prevalence of 25-hydroxycholecalciferol deficiency among their subjects as it is suggested that each antiepileptic drug would independently alter Vitamin D metabolism [26, 27]. That 17% of subjects had insufficient levels of 25-hydroxycholecalciferol levels, highlights the need for closer monitoring and possible supplementation to avert negative effects of poor bone mineralization on the growth of these children.

Children on AED in the present study had a significantly lower mean serum calcium level than the healthy controls and this compares favourably with the findings in an earlier study in 2018 by Sreedharan et al in India [32]. This may be attributed to the similarity in the age range, selection criteria, AED used (Carbamazepine, or Sodium Valproate, though used as monotherapy only), as well as a similar difference in the mean 25-hydroxycholecalciferol levels of the Indian children as in the present study. In addition, the staple food in India consists of mainly rice, millet, noodles, beans, and wheat-based foods, which is similar to the staple food for children in our environment. In contrast, a 2013 study by Razazizzan et al did not note any difference in the mean serum calcium levels between subjects on AED and healthy controls in Iran [33]. Small sample population of the Iranian study may have led to its inability to detect any difference. Maksoud et al in Egypt in 2012 also found no difference in the mean serum calcium level between children on Sodium Valproate and healthy control [34]. The shorter mean duration of therapy of one year in the Egyptian study, as against 2.4 years in the present study, may have accounted for the lack of difference in the mean serum calcium levels, as studies have shown that the effect of the AED usually worsens over time. Besides, the use of a calcium-rich diet in most of the Egyptian subjects on Sodium Valproate may have also accounted for the lack of difference, though the diet of the subjects in the present study was not assessed. The lower mean serum calcium in children on AED in the present study is a risk for poor bone mineralization and may also increase the frequency of their seizures, necessitating either an increase in the dose or number of the AED being administered. This is coupled with the high B-ALP, showing that bone turnover is high reducing the density and increasing risk for osteoporosis later in life. Our report of high B-ALP level in children receiving AEDs was also noted by Voudris et al and like our study, there was no significant association between the duration of therapy and the B-ALP levels. [21]B-ALP is also increased in children with specific bone diseases like Paget, osteogenesis imperfecta, rickets and some malignancies and the fact that the levels were low in healthy controls, substantiates the adverse effect of AEDs on bone health. Titrating the doses of AEDs and/or finding ways of making monotherapy possible may also reduce the effects of the medications on bone health and especially Vitamin D and B-ALP.

5. CONCLUSION

In summary, we have demonstrated that children on AED in UPTH had significantly lower serum calcium and 25-hydroxycholecalciferol levels, as well as significantly higher serum B-ALP levels

than healthy controls with the implication that the medications may have caused this difference. A significant proportion of them had hypocalcaemia as well as subnormal serum 25-hydroxycholecalciferol levels. Antiepileptic drug polytherapy and longer duration of therapy were associated with these abnormalities, but the duration of therapy was the only predictor of these abnormalities. The study, therefore, reiterates the need for regular monitoring of serum 25-hydroxycholecalciferol, calcium, and B-ALP levels in children on antiepileptic drugs, especially for patients on longer duration of therapy.

6. LIMITATIONS

The potential impact of the low serum calcium, and 25-hydroxycholecalciferol levels on bone mineral density (BMD), a feature of the bone structure, could not be evaluated due to the unavailability of dual-energy X-ray absorptiometry (DEXA) in our environment, as it is expensive and inaccessible for now. A future study using Vitamin D with placebo in a randomised controlled trial will also test the effect of AEDs on bone with or without supplementation.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The research and ethics committee of the University of Port Harcourt Teaching Hospital approved the study (UPTH/ADM/90/S.II/VOL.XI/71) August 2016, before commencement and for all subjects and controls, a written informed consent was obtained from the parents before recruitment. The Rivers State schools' management board gave approval before we approached the school for the study. The research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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