ORIGINAL ARTICLE

EFFECTS OF ANTIEPILEPTIC DRUG THERAPY ON 25OH VITAMIN D LEVELS

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Background: Epilepsy is a chronic condition with an incidence of 4–10/1,000 worldwide, Antiepileptic drugs (AED) in common use are carbamazepine (CBZ), phenytoin (DPH), phenobarbitone (PB), and sodium valproate. The effect of AEDs on the vitamin D metabolism is of considerable value especially in children. There are few clinicians who use prophylactic calcium or vitamin D for patients taking AED. The objective of this study was to determine the effect of antiepileptic drugs on vitamin D by measuring 25OH vitamin D levels in patients on AEDs. **Methods:** This case control study was conducted in paediatric department, Fauji Foundation Hospital Rawalpindi. In a duration of 6 months, 34 cases of epileptic children taking CBZ and valproic acid for more than 3 months were selected and 25OH Vitamin D levels were measured and compared with 25OH Vit D levels in healthy controls. **Results:** Out of 34 cases, 11 (32.4%) cases had decreased vitamin D levels (≤20 ηg/dL) whereas 2 (5.9%) had decreased vitamin D levels in control group (p=0.006). **Conclusion:** Antiepileptic drugs negatively effect bone metabolism and increase the risk of osteoporosis, fractures and rickets in children.

Keywords: Epilepsy, Anti epileptic drug therapy, osteoporosis, rickets

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INTRODUCTION

Epilepsy, a disease of nervous system which involves all ages, is most prevalent non-communicable diseases of the world.[1] It is a chronic condition having recurrent seizures triggered from within brain, which occur in the absence of a metabolic-toxic disease.[2] World epidemiologic data place the prevalence of this disease from 4–10/1,000.[3] Antiepileptic drugs (AEDs) are used for prevention of recurrence of seizures. The AEDs in common use are carbamazepine (CBZ), phenytoin (DPH), phenobarbitone (PB), and sodium valproate.[2] Lamotrigine (LTG), Topiramate (TPM), Clobazam (CLB), Oxcarbazepine (OXC) and Levetericitam (LEV) are newer AED's.

At a given time approximately 1% of the population is on long-term and sometimes lifelong, therapy with AEDs and therefore, is exposed to the potential undesirable metabolic side-effects of these drugs. The side-effects involve changes in in homocysteine, lipoproteins and vitamin D metabolism.[4] As multiple health outcomes are dependant on an adequate vitamin D status, the effects of AEDs on vitamin D homeostasis in children is of considerable value. Vitamin D is very important to ensure the proper growth and development of bones in children. Type, dosage and duration of AED treatment determine the exact picture of the osteopathy.[5]

Mainly phenytoin, phenobarbital and carbamezapine have been investigated for their influence on vitamin D metabolism. The commonest theory is that AEDs induce the cytochrome P450 enzymes in liver and cause increased conversion of vitamin D to inactive metabolites there. The inactive vitamin D results in decreased absorption of calcium in the intestines, leading to hypocalcaemia and increase in parathyroid hormone in circulation and increase bone turnover. This in turn causes mineral resorption from bone to keep calcium within normal range for vital functions.[5] These serum biochemical changes in serum which may predispose the individuals to risk of rickets and osteomalacia which usually appear within period of three months of AED monotherapy.[6] Childhood epilepsy is under-resourced and under-treated having a large treatment gap in Pakistan.

The objective of this study was to determine the effect of antiepileptic drugs on vitamin D by measuring 25OH vitamin D levels in patients on AEDs.

MATERIAL AND METHODS

This comparative study was carried out in Paediatric Department, Fauji Foundation Hospital Rawalpindi. Administrative permission from Research and Ethical committee FUMC was obtained, informed consent was taken from parents/guardians.

All patients meeting the inclusion criteria were included in the study and were placed into two equal groups. Group A (cases) included children with uncomplicated idiopathic epilepsy who were on standard recommended doses of either valproic acid or carbamazapine for more than 3 months. Group B was taken as control group including children not taking antiepileptic drugs and matching for age and sex with cases.

Children having kidney disease, hyper-parathyroidism, cancer, gastrointestinal disease, liver

insufficiency, diabetes mellitus, or grave physical abnormalities were excluded from the study. Those on drugs like corticosteroids, taking vitamin D derivatives, or on polytherapy were also excluded.

Age, sex, type of epilepsy, and type and duration of antiepileptics used were recorded. Five ml venous blood was drawn in EDTA bottles and vitamin D levels measured through chemiilluminescent method in Fauji Foundation Hospital, Pathology Laboratory. The results were recorded and documented on pre-designed proforma.

Analysis of data was done using SPSS-17. For the categorical (qualitative) variables, Frequency and percentage were calculated. Mean and standard deviation (SD) were calculated for numerical (quantitative) variables. Chi-square test was used to compare vitamin D levels among cases and controls, and $p<0.05$ was taken as significant.

RESULTS

In Group A mean age of patients was 8.44±2.377 whereas in Group B it was 7.74±2.916 (Table-1). Majority of the children were male (42, 61.8%). Frequency and percentage of male and female in Group A was 26 (76.5%) vs 16 (47.1%) respectively, whereas in Group B it was 8 (23.5%) vs 18 (52.9%) respectively (Table-2).

Mean vitamin-D level in Group A was 52.44±32.891 and in Group B it was 63.76±23.478 respectively (Table-3). Mean dose of drugs of sodium valproate therapy and carbamazepine therapy were 25.96±6.785 and 30±14.142 respectively (Table-4).

Out of 34 cases, 11 (32.4%) had decreased vitamin D levels (≤20 ηg/dL) whereas 2 (5.9%) had decreased vitamin D levels in control group (p=0.006) (Table-5).

Table-1: Descriptive statistics of age in groups

Groups	N	Mean	SD	SEM
Cases	34	8.44	2.377	0.408
Control	34	7.74	2.916	0.500

Table-2: Distribution of gender in groups [n (%)]

Gender	Cases	Control	Total
Male	26 (76.5)	16 (47.1)	42 (61.8)
Female	8 (23.5)	18 (52.9)	26 (38.2)
Total	34 (100)	34 (100)	68 (100)

Table-3: Levels of vitamin D (ηg/dL) in groups

Groups	N	Mean	SD	SEM
Cases	34	52.44	32.891	5.641
Control	34	63.76	23.478	4.026

Table-4: Dosage of AEDs

Groups	N	Mean	SD	SEM
Valproic acid	26	25.96	6.785	1.331
Carbamazapine	2	30.00	14.142	10.000

Table-5: Comparison of vitamin D reduction (≤20 ηg/dL) among cases and controls

Vitamin-D level decreased ≤20 ηg/dL	cases	control	Total
Yes	11 (32.4)	2 (5.9)	13 (19.1)
No	23 (67.6)	32 (94.1)	55 (80.9)
Total	34 (100)	34 (100)	68 (100)

DISCUSSION

With recent estimates of 50 million people suffering from epilepsy globally, along with a rapid rise in the use of antiepileptic medication for other indications, the bone disease related to use of antiepileptic medications is emerging as a severe health risk for millions of people, particularly in childhood, which is the most critical period of bone growth.[7] Osteoporosis is one of the significant chronic clinical conditions that affect about 5% of the population and annually causing 1.5 million fractures in the United States. Patients on anticonvulsive drug therapy are considered as a high-risk group.[8] This study is supporting the evidence that treatment with the anticonvulsant drugs, carbamazepine and sodium valproate can result in serum biochemical abnormalities consistent with hypovitaminosis D in children that is not related to movement disorders or dietary deficiencies.

Two mechanisms are suggested for inactivation of vitamin D by AEDs, hepatic enzyme induction and activation of pregnane X receptor (PXR) and steroid xenobiotic receptors (SXR). All normal physiological adaptive mechanisms in response to progressive 25(OH) D insufficiency and consequent secondary hyper-parathyroidism are promoted by this increased clearance. Hypovitaminosis D results in decreased calcium absorption from the intestine. Thus in the background of low intake of calcium in diet, this hypovitaminosis D caused by AED will have an adverse effect on bone mineral balance. The susceptibility of individuals to the effect of AED on vitamin D and bone metabolism may be influenced by some genetic factors. Direct effect of the drug on intestinal calcium transport includes other mechanisms of AED induced bone loss. For maintenance of aromatase activity necessary in osteoblasts, physiological levels of vitamin D3 are required.

The other proposed mechanisms include inducers of cytochrome P450 enzyme system (for PB, PHT, CBZ), decreased intestinal calcium absorption (for PHT), impaired response to parathyroid hormone (for PB, PHT), secondary hyperparathyroidism, poor vitamin K status (for PHT), calcitonin deficiency, hepatic enzyme inhibition (for VPA), and by induction of the 25-hydroxyvitamin D-24-hydroxylase by the steroid hormone xenobiotic receptor. Multi-drug therapy has shown to be linked with increased risk of bone

mineral metabolic abnormalities as compared to monotherapy.[9]

Similar recent studies show conflicting results regarding decreased vitamin D levels in patients on AEDs. In one study[10] evaluating the effects of carbamazepine or sodium valproate on vitamin D levels prospectively, in 51 ambulatory epileptic children who were followed during the first year of the study, and in 25 and 6 children during the 2nd and 3rd year, respectively, 49% patients were reported to develop hypovitaminosis D during the study period. The results are supporting our findings. In another multi-centre cross-sectional study on otherwise healthy children who were on monotherapy with valproic acid, oxcarbazepine, lamotrigine, sulthiame, levetiracetam, or topiramate for at least 6 months data on calcium, phosphorus, alkaline phosphatase, 25-OH vitamin D, and parathormone were collected. Among 128 patients, 24.4% had hypocalcemia, 25.4% hypophosphatemia, and 13.3% had 25-OH vitamin D levels <10 ηg/dL.[8]

Children with epilepsy seen in a tertiary neurology clinic in Queensland Australia were contacted requesting bone health blood tests during winter of 2011. Vitamin D deficiency was identified in 24 (22%) of 111, and an additional 45 (41%) of 111 had vitamin D insufficiency. Multiple logistic regression analysis identified children on >2 antiepileptic drugs or with underlying genetic aetiologies to be more likely to have vitamin D deficiency.[10]

CONCLUSION

Antiepileptics do affect the bone mineral metabolism adversely, as manifested by decreased vitamin D levels in serum of patients taking antiepileptic drugs. Vitamin D and calcium supplementation should be started with AED therapy. Further studies should be done in which a baseline vitamin D level before initiation of AED therapy should be measured. Other markers of bone metabolism like serum calcium, phosphate, alkaline phosphatase, and BMD should also be studied.

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