

Effect of Anti-Convulsant Drugs on Bone Metabolism in Pediatric Epileptic Patients

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¹ Conception of study

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Abstract

Objective: Epilepsy is a common neurological disorder in children requiring long-term therapy using anti-epileptic drugs (AEDs). Chronic use of AEDs may impair bone health. This study aimed to determine the biochemical changes affecting bone metabolism in pediatric epileptic patients taking AEDs.

Materials and Methods: This cross-sectional study was conducted in the Department of Pediatrics of Benazir Bhutto Hospital, Rawalpindi from January 2019 to July 2019. A total of 95 children were enrolled based on a non-probability consecutive sampling technique. Bone metabolism was evaluated by measuring serum calcium and alkaline phosphatase levels in all the study participants. Data was entered on SPSS v 22 and descriptive statistics were applied.

Results: Of 95 epileptic children, 50.53% (n=48) were male and 49.47% (n=47) were females taking AEDs (either carbamazepine, valproate sodium, or phenobarbital), 47.37% (n=45) were between 2-6 years of age while 52.63% (n=50) were between 7-11 years of age (Mean age: 6.53±2.54 years). The mean calcium and alkaline phosphatase levels of patients were calculated as 7.94±2.3 mg/dl and 226.31±17.45 IU/L respectively. The frequency of hypocalcemia in patients taking AEDs was recorded in 67.37% (n=64) and 81.05% (n=77) had raised alkaline phosphatase levels.

Conclusion: This study concludes that the frequency of hypocalcemia and raised alkaline phosphatase levels in patients taking AEDs is higher and needs attention to address this issue while the magnitude recorded in this study is primarily in the local population which needs to be re-assessed through multi-center trials.

Keywords: Epilepsy, Antiepileptic Drugs, Hypocalcemia, Alkaline Phosphatase Levels.

Introduction

Epilepsy is a chronic neurological disorder, characterized by recurrent seizures due to disruptions of electrical signals in the brain, affecting all age groups requiring long-term therapy using antiepileptic drugs (AEDs).¹ It is estimated that over 70 million people worldwide are affected by this disorder with a prevalence of 15.5 to 23 per 1000 children in Pakistan.^{2,3}

Chronic use of AEDs is associated with several problems including behavioral disorders, psychiatric disorders, metabolic and endocrine disorders, idiosyncratic reactions, and drug interaction effects.⁴ Besides, some studies reported that patients with epilepsy treated with AEDs have an increased risk of fractures, low bone mineral density (BMD), and abnormalities in bone metabolism^{5,6} however, skeletal diseases associated with long-term AED treatment are seriously unrecognized. A survey of adult and pediatric neurologist showed that only 28% of adult and 41% of pediatric neurologists screen their patients for bone diseases.⁷ This showed a lack of consensus between treating physicians about impact of AED therapy on bone that may put epileptic patients at risk especially children, regarding bone health or developing bone diseases.

Bone abnormalities such as short height, abnormal dentition, rickets, and osteomalacia have been reported to be linked to the use of AEDs.^{8,9} The mechanisms through which AEDs cause abnormal bone metabolism and increase fractures are not fully understood. Studies have shown that hypocalcemia is an important biochemical abnormality in patients receiving Cytochrome P450 enzyme-inducing AEDs (such as carbamazepine, phenytoin sodium, phenobarbital and valproic acid), which potentially increase the catabolism of vitamin D to inactive metabolites, leading to reduction of calcium.¹⁰ However, some non-enzyme-reducing AEDs have also been linked with low bone mass.¹¹ 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 metabolism in pediatric patients with epilepsy.

The maintenance of growth and bone health is a complex 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 bone metabolism, clinical parameters such as serum calcium (Ca) and alkaline phosphatase levels (ALP) may reveal abnormalities after AED therapy in pediatric patients with epilepsy.¹² As no local statistics exist on the effect of AEDs on bone metabolism, this study aimed to provide data on the influence of AEDs on bone metabolism in otherwise healthy ambulatory children with epilepsy on chronic anticonvulsive monotherapy with a particular focus on sodium valproate, carbamazepine, and phenobarbitone.

Materials and Methods

This cross-sectional study was conducted at the Pediatric Department of Benazir Bhutto Hospital Rawalpindi from January 2016 to July 2016. Ambulatory children between 2 and 11 years of age with epilepsy on monotherapy for at least 6 months with either sodium valproate (10-60 mg/dl), carbamazepine (10-35 mg/dl), phenobarbitone (5-7 mg/dl) were included. Exclusion criteria were acute or chronic disease affecting bone metabolism, immobility, lack of ambulatory gait, endocrinologic diseases, concomitant medication (steroids or immunosuppressant), or any other comorbidity like muscular dystrophy, other neurologic conditions, or recent osteomyelitis. The study was approved by the Institutional Research Committee and Ethical Review Committee and both verbal and written informed consent was obtained from all parents/guardians after explaining the importance of the study.

All patients were subjected to complete history taking (including, age, sex, type of epilepsy, age of onset of the disease, type, age of onset of the drugs, and complication of treatment) and detailed clinical examination (including general and complete neurological examination).

The studied subjects were assessed for serum level of Ca and ALP; About 3 ml of venous blood were withdrawn from each child by sterile venipuncture and allowed to clot at 37 °C, separated after centrifugation at 3000 rpm for 10 min, the separated serum used for determination of serum total calcium and alkaline phosphatase using fully automated

chemistry analyzer (COBAS 6000 CCE (Roche Diagnostics Deutschland; Mannheim, Germany). The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 22. Descriptive statistics were done for numerical variables (age, levels of calcium and alkaline phosphatase) by mean and standard deviation, while they were done for categorical variables (children with hypocalcaemia and increased levels of alkaline phosphatase) by number and percentage. Effect modifiers like age, gender and socio-economics status were controlled by stratification. The post stratification chi-square test was used with $P \leq 0.05$ and were considered statistically significant.

Results

A total of 95 epileptic children who fulfil the inclusion criteria were enrolled in the study of which 50.53% (n=48) were male and 49.47% (n=47) were females taking AEDs (either carbamazepine, valproate sodium or phenobarbital), 47.37% (n=45) were between 2-6 years of age while 52.63% (n=50) were between 7-11 years of age. Mean age was calculated as 6.53±2.54 years as shown in Table 1.

Table 1: Clinical characteristics of the study subjects

Parameters	N (%)	Mean ± SD
Age		
2-6 years	45 (47.37)	6.53±2.54
7-11 years	50 (52.63)	
Gender		
Male	48 (50.53)	-
Female	47 (49.47)	
Type of seizures		
Generalized	56 (58.94)	-
Partial	39 (41.05)	

Mean calcium and alkaline phosphatase levels of patients were calculated as 7.94±2.3 mg/dl and 226.31±17.45 IU/L respectively. Frequency of hypocalcemia in patients taking AEDs was recorded in 67.37% (n=64) and 81.05% (n=77) had raised alkaline phosphatase levels whereas 32.63% (n=31) had no findings of the morbidity as shown in Table 2.

Table 2: Frequency of Calcium levels and ALP in patients taking AEDs.

Variables	Yes (%)	No (%)
Hypocalcemia	64 (67.37)	31 (32.63)
Raised ALP	77 (81.05)	18 (18.94)

Effect modifiers like age, gender and socio-economics status were controlled by stratification. Post stratification chi-square test was applied where P value ≤ 0.05 was considered significant (Table 3).

Table 3: Stratification for frequency of hypocalcemia and raised ALP levels with respect to age and gender.

Variables	Hypocalcemia		P-value	Raised ALP		P-value
	Yes	No		Yes	No	
Age			0.76			0.77
2-6						
7-11	31	14		37	8	
	33	17		40	10	
Gender			0.77			0.27
Male	33	15		41	7	
Female	31	16		36	11	

Discussion

Epilepsy is a common neurological disorder worldwide and anti-epileptic drugs (AEDs) are always the first choice for treatment. However, more than 50% of patients with epilepsy who take AEDs have reported bone abnormalities.

As the effect of antiepileptics on serum calcium and alkaline phosphatase is controversial and no local statistics exist one effect of antiepileptic drugs on bone. This study is helpful to determine the adverse effects of these drugs on bones and to formulate guidelines regarding calcium and vitamin D supplements.

We compared our results with a previous study conducted in India showing that 61% of children had hypocalcemia and 79% had elevated alkaline phosphatase levels with chronic use of antiepileptic drugs.¹⁴ According to a study conducted in department of neurosurgery, AL Zahra university Hospital valproate therapy does not seem to change bone turnover in adult patients taking antiepileptics.¹⁵

Erbayat Altay and colleagues assessed lumbar spine (L2-4) and femoral neck bone mineral density (BMD) in 36 children taking either carbamazepine or valproic acid for longer than one year, for generalized idiopathic epilepsy. They recorded that serum levels of calcium were subnormal and alkaline phosphatase levels were high in the carbamazepine group. They concluded that valproic acid and carbamazepine monotherapies have minimal effects on bone mineral metabolism, but routine monitoring of risk and consideration of prophylactic vitamin D supplementation is important.¹⁶

Conclusion

This study concluded that the frequency of hypocalcemia and raised alkaline phosphatase levels in patients taking antiepileptic drugs is higher and needs attention to address this issue while the magnitude recorded in our study is primary in local population which needs to be re-assessed through multi-centre trials.

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