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Prevalence of Hypocalcemia and Raised Serum Alkaline Phosphatase Levels Among Children Taking Antiepileptic Drugs

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ABSTRACT

Background: Epilepsy in children is treated by antiepileptic drugs, which cause imbalances of mineral metabolism such as hypocalcemia and acquired elevated alkaline phosphatase levels. These biochemical markers need careful monitoring to interpret the long-term outcomes of the treatment of AED. **Objective:** To determine the frequency of hypocalcemia and raised serum alkaline phosphatase among children with epilepsy taking anti-epileptic drugs in a tertiary care hospital. **Study Design:** Descriptive cross-sectional study. **Duration and Place of Study:** The study was conducted from November 2023 to May 2024 at the Department of Pediatrics, POF Hospital, Wah Cantt. **Methodology:** A total of 91 children aged 3 to15 years, diagnosed with epilepsy and receiving AEDs for at least six months, were included in the study. Serum calcium and ALP levels were measured, and their prevalence was assessed. **Results:** The mean age of the patients was 8.76 ± 3.30 years, with 67% of children shown hypocalcemia and 69.2% showing elevated ALP levels. The prevalence of hypocalcemia was highest in children on phenobarbital (84%), followed by valproic acid (71.4%) and carbamazepine (48.4%). **Conclusion:** Our study found a strong link between chronic antiepileptic drug (AED) use and bone metabolism disturbances, such as elevated alkaline phosphatase and hypocalcemia. Classical AEDs like valproic acid and phenobarbital significantly affect bone health. Regular monitoring of children on long-term AEDs is recommended, with possible vitamin D and calcium supplementation. Further research with larger, multi-centered populations is needed to validate these findings and guide appropriate interventions..

INTRODUCTION

Epilepsy is a neurological disorder that consists of repeated seizures due to abnormal electrical activity of the brain.[1] It is one of the most common child neurological conditions that affect as many as a million children worldwide.[2] Seizures could be a simple loss of consciousness or a severe convulsion and of different frequency and intensity. Childhood epilepsy might have a profound impact on the child's development and education as well as social interactions.[3] The cause of epilepsy in children could vary from a congenital cause to a head injury, infection, or metabolic conditions.[4] Effective management of epilepsy might entail treatment for the rest of the child's life by the use of antiepileptic drugs (AEDs) to prevent and control seizures.[5] While the AEDs are very effective as far as the management of epilepsy is concerned, the drugs are by no means side-effect-free and should be carefully monitored.[5]

Antiepileptic drugs such as Carbamazepine, Valproic acid, and Phenobarbital are commonly prescribed as a way of controlling seizures among children suffering from epilepsy.[6] All the drugs work differently within the brain as a way of reducing or preventing seizures. Carbamazepine may function as a treatment of partial and generalized seizures through the stabilization of the electrical activity within the brain.[7] Valproic acid acts by creating a higher level of gamma-aminobutyric acid (GABA) within the brain as a way of inhibiting seizures.[7] Phenobarbital works as a barbiturate and exerts a sedative action while complementing the inhibiting activity of GABA.[7] While the drugs work effectively, they have a wide variety of side effects.

Hypocalcemia occurs as a side effect of chronic treatment by antiepileptic drugs, most frequently among children undergoing treatment by drugs such as Carbamazepine and Valproic acid.[8] The cause of the side effect is suspected through the process by which the drugs disrupt the metabolism of the mineral calcium within the body. Antiepileptic drugs disrupt the liver's ability to metabolize vitamin D as a necessary nutrient for the absorption of the mineral by the intestines.[9] The

inhibited absorption of the mineral results in lower levels of the electrolyte within the circulatory system and thus hypocalcemia. The disorder results in a variety of symptoms including cramps as well as irritability and severe conditions such as deformity and fracture of the bone.[10]

Elevated serum alkaline phosphatase (ALP) levels are a side effect of antiepileptic drug (AED) long-term intake.[11] Alkaline phosphatase is a resident enzyme of the liver tissues, the bones, and the kidneys and elevated levels of the enzyme in the blood are typically indicative of liver or bone malfunction.[12] The ability of the AEDs, particularly Carbamazepine, Valproic acid, and Phenobarbital, to promote production of ALP by the malfunctioning of the liver and the metabolism of the bones contributes to the elevated levels of ALP.[13] The liver malfunction produced by the intake of the AEDs leads to increased levels of the ALP due to the inefficiency of the liver in metabolizing enzymes.[14]

A recent study conducted by Zia T and colleagues investigated the prevalence of hypocalcemia and increased alkaline phosphatase (ALP) levels in children using antiepileptic drugs (AEDs). The results revealed that 62% of the patients exhibited hypocalcemia, while 75% of the children showed elevated ALP levels.[15]

Despite being effective for epilepsy management, the side effects such as hypocalcemia and the level of elevated serum alkaline phosphatase (ALP) among the pediatric population remain under investigated. It is necessary to understand the conditions' incidence for the reason of aiding in the detection and intervention at the initial stages as well as developing ways of preventing the side effects' implications. It is anticipated that by bridging the existing knowledge gap, children's epilepsy management will be improved and evidence-based management approaches will be established.

METHODOLOGY

This descriptive cross-sectional study was conducted from November 2023 to May 2024 in the Department of Pediatrics at POF Hospital, Wah Cantt. A total of 91 children with epilepsy were included. The sample size was determined using the WHO sample size calculator, with a 95% confidence level, 10% absolute precision, and an anticipated population proportion of 62%.[15]

Inclusion criteria consisted of children diagnosed with epilepsy and receiving AEDs for at least six months, aged between 3 and 15 years, of both genders. AEDs are defined as the commonly prescribed medications to control epilepsy, including Carbamazepine, Valproic acid, and Phenobarbital. Exclusion criteria included children with cerebral palsy, those receiving calcium therapy within the past 15 days, individuals with thyroid or hematologic disorders, children with physical disabilities, those with renal or liver failure, and children on immunosuppressant drugs or steroids. Children with incomplete clinical histories were also excluded.

A detailed clinical examination was conducted by the trainee researcher, and necessary medical history, including the medication and duration of the illness, was documented. Blood samples were collected using an aseptic technique, and 5 ml of blood was drawn for serum calcium and ALP analysis. Hypocalcemia was diagnosed if the serum calcium level was found to be below 8.5 mg/dl. Similarly, elevated ALP was diagnosed if the serum alkaline phosphatase level exceeded 300 IU/L. These measurements were analyzed in the hospital laboratory. The collected data was entered and analyzed using IBM SPSS version 25.0. Descriptive statistics were employed, with qualitative variables such as gender, residential status, type of AED used, hypocalcemia, and raised ALP reported as frequencies and percentages. Quantitative variables, including age, duration of illness, duration of AED use, serum calcium levels, and serum ALP levels, were presented as mean ± standard deviation. Stratification was used to control for effect modifiers such as age, gender, AED type, duration of illness, and therapy duration. A chi-square test was applied post-stratification, and a p-value ≤ 0.05 was considered statistically significant.

RESULTS

As seen in Table-I, the mean age of participants was 8.76±3.30 years, with a mean body mass index (BMI) of 17.95±2.08 kg/m². The mean duration of illness was 27.11±13.96 months, while the mean duration of AED use was 24.71±13.27 months. The mean serum calcium level was 8.39±0.30 mg/dl, and the mean serum ALP level was 313.34±22.07 IU/L. The gender distribution showed that 51.6% were male and 48.4% were female, with 64.8% residing in urban areas. The most commonly prescribed AED was valproic acid (38.5%), followed by carbamazepine (34.1%) and phenobarbital (27.5%).

Table I

Patient Demographics

Demographics		Mean ± SD
Age (years)		8.76±3.30
BMI (Kg/m²)		17.95±2.08
Duration of Illness (months)		27.11±13.96
Duration of AEDs use (months)		24.71±13.27
Serum Calcium Level (mg/dl)		8.39±0.30
Serum ALP (IU/L)		313.34±22.07
Gender	Male n (%)	47 (51.6%)
	Female n (%)	44 (48.4%)
Residential Status	Rural n (%)	32 (35.2%)
	Urban n (%)	59 (64.8%)
Type of Antiepileptic Drug	Carbamazepine n (%)	31 (34.1%)
	Valproic acid n (%)	35 (38.5%)
	Phenobarbital n (%)	25 (27.5%)

In Table-II, the prevalence of hypocalcemia was found to be 67%, while 69.2% of the children had raised ALP levels.

Table II

Frequency of Abnormal Laboratory Parameters

Laboratory Parameter	Frequency	% age
Hypocalcemia	61	67%
Raised ALP	63	69.2%

Table-III presents the association of hypocalcemia with demographic factors. The prevalence of hypocalcemia was 71.9% in children aged ≤10 years, compared to 55.6% in those aged >10 years, with a p-value of 0.13. Gender did not significantly impact hypocalcemia prevalence (p = 0.264), with 61.7% of males and 72.7% of females exhibiting hypocalcemia. The duration of illness and AED use showed no significant correlation with hypocalcemia (p-values of 0.805 and 0.594, respectively). However, a significant association was found between hypocalcemia and the type of AED used (p = 0.015), with the highest prevalence observed in children on phenobarbital (84%), followed by valproic acid (71.4%) and carbamazepine (48.4%).

Table III

Association of Hypocalcemia with Demographic Factors

Demographic Factors		Hypocalcemia		p-value
		Yes n(%)	No n(%)	
Age (years)	≤10	46 (71.9%)	18 (28.1%)	0.13
	>10	15 (55.6%)	12 (44.4%)	
Gender	Male	29 (61.7%)	18 (38.3%)	0.264
	Female	32 (72.7%)	12 (27.3%)	
Illness Duration (months)	≤20	24 (68.6%)	11 (31.4%)	0.805
	>20	37 (66.1%)	19 (33.9%)	
AEDs Duration (months)	≤20	28 (70.0%)	12 (30.0%)	0.594
	>20	33 (64.7%)	18 (35.3%)	
Type of Antiepileptic Drug	Carbamazepine	15 (48.4%)	16 (51.6%)	0.015*
	Valproic acid	25 (71.4%)	10 (28.6%)	
	Phenobarbital	21 (84.0%)	4 (16.0%)	

***Fischer Exact Test**

Table-IV presents the association of raised ALP with demographic factors. While age showed a borderline trend (p = 0.066), with 75% of children ≤10 years having raised ALP compared to 55.6% of those >10 years, the result did not reach statistical significance. Gender did not significantly influence raised ALP levels (p = 0.484), with 66% of males and 72.7% of females having raised ALP levels. Duration of illness and AED usage were not significantly associated with raised ALP, with p-values of 0.914 and 0.888, respectively. However, the type of AED was significantly associated with raised ALP levels (p = 0.008), with the highest prevalence in children using phenobarbital (84%), followed by valproic acid (77.1%) and carbamazepine (48.4%).

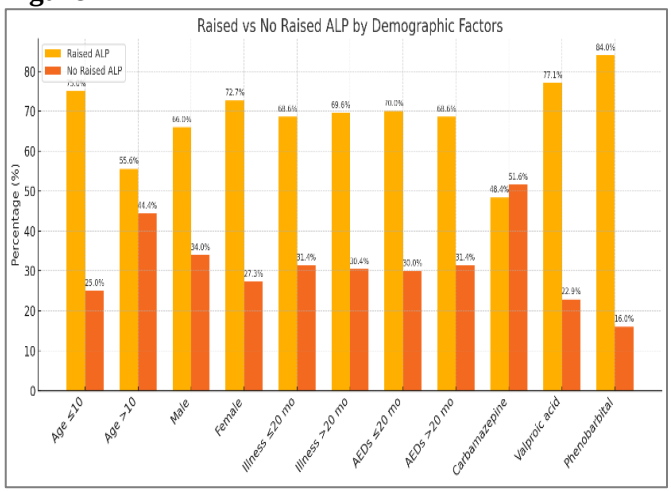
Table IV

Association of Raised ALP with Demographic Factors

Demographic Factors		Raised ALP		p-value
		Yes n(%)	No n(%)	
Age (years)	≤10	48 (75.0%)	16 (25.0%)	0.066
	>10	15 (55.6%)	12 (44.4%)	
Gender	Male	31 (66.0%)	16 (34.0%)	0.484
	Female	32 (72.7%)	12 (27.3%)	
Illness Duration (months)	≤20	24 (68.6%)	11 (31.4%)	0.914
	>20	39 (69.6%)	17 (30.4%)	
AEDs Duration (months)	≤20	28 (70.0%)	12 (30.0%)	0.888
	>20	35 (68.6%)	16 (31.4%)	
Type of Antiepileptic Drug	Carbamazepine	15 (48.4%)	16 (51.6%)	0.008*
	Valproic acid	27 (77.1%)	8 (22.9%)	
	Phenobarbital	21 (84.0%)	4 (16.0%)	

***Fischer Exact Test**

Figure 1



DISCUSSION

The results show a high prevalence of both conditions as 67% of the children were having hypocalcemia and 69.2% of the children having elevated levels of the enzyme ALP. The finding aligns with literature evidence that shows that such AEDs as phenobarbital cause disturbance of mineral metabolism resulting in decreased serum levels of calcium. The children undergoing treatment using the AEDs are typically noted for having hypocalcemia as a result of disturbance of the metabolism of the vitamin D that results in the failure of

absorption of the calcium. The elevated levels of the enzyme ALP are equally consistent with the bone turnover disturbance as a result of the chronic use of the drugs, particularly of the drug phenobarbital, a drug that affects the mineralization of the bone. The statistiscal relationship of the type of the drug AED and the development of both hypocalcemia as well as the elevated levels of the enzyme ALP, particularly of the drug phenobarbital, justifies the monitoring of the children on the drug for these laboratory abnormalities.

Our mean age was 8.76±3.30 years and mean serum calcium was 8.39±0.30 mg/dl while the mean serum ALP was 313.34±22.07 IU/L. The finding tallies with Rani et al. [16] whereby they produced the same finding among the pediatric cases where the mean serum calcium was 7.94±2.3 mg/dl and elevated level of the ALP was 226.31±17.45 IU/L. The two studies present a considerable number of cases of hypocalcemia at 67% and 67.37% for our article and Rani et al.'s article respectively, calling attention to the commonality of the decreased level of the calcium among children on the AEDs. The elevated level of the ALP demonstrated by the two studies indicates the derangement of the metabolism of the bones caused by the prolonged application of the AEDs and signifies that the AEDs have the capacity of disturbing the body's homoeostasis of the calcium as well as the turnover of the body's bones.

Our findings revealed a significant correlation between hypocalcemia and the type of AED administered, most prominent under phenobarbital (84%) followed by valproic acid (71.4%) and then carbamazepine (48.4%). Our finding draws a comparison with the work of Jafer et al. [17] who noted a prevailing hypocalcemia among patients on older AEDs such as Carbamazepine and Valproate. The implication of this finding aligns with the hypothesis that the older AEDs have a stronger impact on the metabolism of calcium as opposed to the newer versions such as Levetiracetam. The replicate finding across the two studies implies a dose-dependent impact of the drugs on metabolism of the bones such that the old drugs cause a higher degree of disturbance of the mineral balance as opposed to the new drugs.

Of the issue of raised ALP prevalence, our work revealed 69.2% of the participants having increased levels of the marker, consistent with the finding of Gupta et al. [18] that 75% of children on AEDs have elevated ALP levels. Our work and theirs confirm the association of long-term use of AEDs and elevated ALP as a marker of turnover. Yet our work failed to demonstrate a correlation between the length of illness or of the use of AEDs and elevated levels of ALP (p-values of 0.914 and 0.888, respectively), unlike Gupta et al. [18] who noted a positive correlation between the length of AED treatment and alkaline phosphatase. The difference between the two studies may have arisen due to differing populations and methodologies used, including our use of a more diverse pediatric population, as opposed to the specific patient group of longer-term AED treatment by Gupta et al.

One interesting aspect of our findings is that age showed a borderline trend for influencing raised ALP levels, with 75% of children aged ≤10 years having elevated ALP compared to 55.6% in those aged >10 years. This result mirrors the findings of Schmitt et al. [19] who found similar trends in adults receiving long-term anticonvulsant therapy, indicating that the impact of AEDs on bone metabolism may vary with age. However, the lack of statistical significance in both studies suggests that other factors, such as the specific AED used or underlying genetic and environmental factors, may play a more crucial role in determining ALP levels than age alone.

While the findings of the present study highlight the frequency of hypocalcemia and derangement of alkaline phosphatase levels, additional studies are needed to elucidate the long-term implications of these biochemical abnormalities on fracture risk and bone mineral content. Future studies incorporating larger cohorts involving multiple sites would be more generalizable regarding the effects of AEDs on bone metabolism on a wider population.

Several limitations of this study should be highlighted. The fact that it was a single-centre study implies that the results may not be generalizable to populations or regions outside. The small sample number could lower the statistical power of some of the analyses. The cross-sectional design of the study implies that we cannot make cause-and-effect conclusions about the relationship between the use of the AEDs and the abnormality of the metabolism of the bones. The contribution of additional variables such as the nutrition factors or the genetic factors towards the health of the bone was not investigated extensively. The follow-up was short-term at one year and may not be long enough to pick up the full range of the changes of the health of the bone over time.

CONCLUSION

Our study has concluded a close correlation between chronic treatment of antiepileptic drugs (AEDs) and derangements of the metabolism of the bones as indicated by alkaline phosphatase elevation and hypocalcemia. The outcomes show the significant role of the treatment of AEDs on the health of the bones, particularly by the classical drugs such as valproic acid and phenobarbital. Because of the commonality of these

laboratory derangements, our recommendation is that health providers monitor the health of children under chronic treatment of AEDs on a regular basis for potential intervention such as supplementation of vitamin D and calcium. It will be needed that the outcomes are verified on larger and multi-centered populations.

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