

EVALUATION OF EFFECTS OF ANTI-EPILEPTIC DRUGS ON BONE MINERAL DENSITY IN EPILEPTIC CHILDREN

Dr. Asha Shirahatti¹, Dr Trishala Shirahatti², Dr. Savita Kadam³, Dr. Amruta Shirahatti⁴

Dr Someshwar A Kandagal⁵

¹MD Anatomy, Assistant Professor, Department of Anatomy, KAHER'S J.N. Medical College, Belagavi.

²MD DNB Dermatology, Senior resident, Department of Dermatology, St Johns medical college hospital, Bangalore

³MBBS, DCH, DNB Paediatrics, Assistant Professor, Department of Paediatrics, Government Medical College and Hospital, Miraj

Corresponding author:

Dr. Amruta Shirahatti

MBBS, DCH, DNB Paediatrics, Fellowship in Paediatric Neurology

Senior Resident

Department of Paediatric Neurology

KAHER'S J.N. Medical College, Belagavi

amrutashirahatti3@gmail.com

Dr Someshwar A Kandagal

MD DNB General Medicine

DrNB resident

Department of medical Gastroenterology

Manipal hospital Bangalore

KEYWORDS

ABSTRACT:

INTRODUCTION

Epilepsy is a common medical and social disorder characterized by epileptic seizures. The brain's electrical signals are disrupted, which causes these seizures. Seizures result from these disturbances, which momentarily impair nerve cell communication. Additional potential pathways include a direct impact on bone cells, such as calcitonin insufficiency, hypoparathyroidism, and decreased calcium absorption and decreased responsiveness to parathyroid hormone. The connection between AEDs and bone disease has been explained by a number of theories. Furthermore, extending the anti-epileptic medication course may raise the risk of osteopenia and fractures.

MATERIALS AND METHODS

This is a Prospective Comparative Study was conducted in tertiary care centre at Dr. Bidari's Ashwini Hospital, Vijayapur, Karnataka with a study period of 1 year. All children with epilepsy with age group 1-14 years on AEDs were included in this study. Children with severe protein energy malnutrition, on calcium or vitamin D supplementation and with metabolic bone diseases were excluded. Written informed consent was taken from the parents/guardian. Laboratory investigations of serum calcium, serum phosphorus, serum alkaline phosphatase and vitamin D and radiological investigation DEXA scan- dual energy x-ray absorptiometry scan were done.

RESULTS

The cases and controls were taken randomly and we found that maximum number of cases and controls fall in 6-10 years of age group. In current study 20% of the epileptic children on AEDs were having below normal serum calcium level while serum calcium level in healthy control is normal. In our study 18.3% of the epileptic children on AEDs were having below normal serum phosphorus level while serum phosphorus level in healthy control is normal. Total 30% of the epileptic children on AEDs were having above normal serum alkaline phosphatase level for age while serum alkaline phosphatase level in healthy control is normal for age. In this study 13.3% of the epileptic children on AEDs were having below normal bone mineral density level (DEXA scan showing lower than normal limits) while bone mineral density in healthy control is normal.

From this study 33.3% of the cases on poly therapy showed below normal bone mineral density level compared to 4.8% cases on mono therapy showed below normal bone mineral density level.

CONCLUSION

The most often used AED is sodium valproate, which is followed by levetiracetam. Serum calcium, serum phosphorus and vitamin D levels are significantly lower in epileptic children with prolonged anti-epileptic therapy. Serum alkaline phosphatase level is significantly higher in epileptic children with prolonged anti-epileptic therapy. BMD by DEXA scan is significantly lower in epileptic children with prolonged anti-epileptic therapy.

Keywords: Anti-Epileptic Drugs, Bone Mineral Density, Epileptic Children

INTRODUCTION

Epilepsy is derived from Greek term 'Epilepsia'- 'to seize'. Two or more unprovoked seizures are defined as epilepsy. Incidence: 4–7% of children have seizures. Epilepsy affects 4–8 out of every 1000 people. The brain's electrical signals are disrupted, which causes these seizures. Seizures result from these disturbances, which momentarily impair nerve cell communication [1]. Additional potential pathways include a direct impact on bone cells, such as calcitonin insufficiency, hypo-parathyroidism, and decreased calcium absorption and inhibition of response to parathyroid hormone.

Numerous studies have shown that children with epilepsy had significantly lower bone mineral density (BMD), particularly on receiving polytherapy treatment as opposed to only one anti-epileptic medication [2]. Bone density, as indicated by calcium content, is measured by bone mineral density (BMD). Most of the children need to take anti-epileptic medications (AEDs) for a long period, perhaps for the rest of their lives. AEDs are linked to serious adverse consequences that go beyond radiological signs of rickets, such as decreased bone mineral density, altered bone turnover, and an increased risk of fracture [3].

The connection between AEDs and bone disease has been explained by a number of theories. Numerous AEDs stimulate the metabolism of cytochrome P450 in the liver. Low vitamin D levels have been hypothesized to be caused by these AEDs increasing the hepatic metabolism of vitamin D (Vit D) [4]. However, non-enzyme inducing AEDs have also been associated with low vitamin D levels and in turn with poor bone health. Therefore, although the newer AEDs are less potent enzyme inducers than older AEDs, they are not necessarily inert in bone metabolism. Studies have reported variable changes in BMD and vitamin D levels in children taking AEDs(5).

Furthermore, extending the anti-epileptic medication course may raise the risk of osteopenia and fractures. [6] Because bone loss happens gradually and without symptoms, osteopenia is regarded as a silent illness. It happens as a result of insufficient bone mineralization [7]. Osteomalacia raises the chance of fracture. Many of the consequences of osteomalacia coincide with those of osteoporosis. Bone mineralization starts at birth and reaches a plateau in the third decade of life, followed by steady bone loss as a natural aging process [8]. These findings have raised the need for improved diagnosis and treatment methods, like as laboratory testing and DEXA (Dual-energy X-ray absorptiometry) scans, to address children's bone health [9].

The specific beam filtering and near-perfect spatial registration of the two attenuations required for DEXA make it a unique imaging modality that is often unavailable on general-purpose x-ray equipment. Bone mass and soft tissue composition may be measured by scanning the entire body [10,11]. Children using AEDs have a variety of biochemical anomalies related to bone metabolism. These abnormalities include decreased blood levels of physiologically active vitamin D metabolism, hypomagnesemia, and hypocalcemia. Furthermore, there are increased levels of indicators of bone turnover, including serum alkaline phosphatase and indicators of bone production and resorption. A radiological investigation using a DEXA scan can identify the decrease in bone mineral density.

MATERIALS AND METHODS

This is a Prospective Comparative Study was conducted in tertiary care centre at Dr. Bidari's Ashwini Hospital, Vijayapur, Karnataka from From 1/7/2020 to 30/6/2021.

INCLUSION CRITERIA

Group 1: All children with epilepsy with age group of 1-14 years on anti-epileptic drugs for more than 1 year.

Group 2: Normal healthy children not on anti-epileptic drugs.

EXCLUSION CRITERIA

For both group 1 and group 2

- Children with severe protein energy malnutrition
- Children on calcium or vitamin D supplementation
- Children with metabolic bone diseases

GROUP 1- Children with epilepsy on anti-epileptic drugs.

GROUP 2- Normal healthy children not on anti-epileptic drugs.

METHODOLOGY

All children with epilepsy with age group 1-14 years on AEDs for more than 1 year of duration will be considered for this study. Written informed consent will be taken from the parents/guardian. Laboratory investigations of serum calcium, serum phosphorus, serum alkaline phosphatase and vitamin D and radiological investigation DEXA scan- dual energy x-ray absorptiometry scan was done.

RESULTS

Table 1 : Distribution Of Age Between Cases And Controls

Age(yrs)	EC group(Cases)		Controls	
	N	%	N	%
1-2	0	0.0%	4	10.0%
2-4	6	10.0%	8	20.0%
4-6	8	13.3%	6	15.0%
6-8	15	25.0%	11	27.5%
8-10	17	28.3%	7	17.5%
>10	14	23.3%	4	10.0%
Total	60	100.0%	40	100.0%

The cases and controls were taken randomly and we found that maximum number of cases and controls fall in 6-10 years of age group.

Table 2 : Distribution Of Sex Between Cases And Controls

Sex	EC group		Controls	
	N	%	N	%
Male	42	70.0%	23	57.5%
Female	18	30.0%	17	42.5%
Total	60	100.0%	40	100.0%

Male predominance is there both in cases(70%) and controls(57.5%)

Table 3 : Distribution of Cases according to type of Epilepsy

Type of Epilepsy	N	%
Focal Tonic	6	10.0%
Focal Clonic	2	3.3%
Focal Atonic	2	3.3%
Focal Myoclonic	1	1.7%
Generalised Tonic clonic	34	56.7%
Generalised Tonic	5	8.3%
Generalised Clonic	5	8.3%
Generalised Atonic	4	6.7%
Generalised Myoclonic	1	1.7%
Total	60	100.0%

56.7% of the cases were generalized tonic clonic seizures followed by 10% of focal tonic seizures.

Table 4: Distribution Of Cases According To Type Of Aeds

Type of AEDs	N	%
Sodium valproate	21	35.0%
Levetiracetam	11	18.3%
Carbamazepine	7	11.7%
Sodium valproate, Clobazam	6	10.0%
Sodium valproate, Levetiracetam	5	8.3%
Oxcarbazepine	3	5.0%
Phenobarbitone, Sodium valproate	2	3.3%
Phenytoin sodium, Sodium valproate	2	3.3%
Carbamazepine, Sodium valproate	1	1.7%
Levetiracetam, Clobazam	1	1.7%
Sodium valproate, Phenobarbitone	1	1.7%
Total	60	100.0%

Majority of epileptic children were on Sodium valproate(35%) followed by Levetiracetam (8.3%).

Table 5: Sr. Calcium Levels Between Cases And Controls

Sr. Calcium (mg/dl)	EC group		Controls		p value
	N	%	N	%	
Below the normal	12	20.0%	0	0.0%	0.003*
Normal	48	80.0%	40	100.0%	
Total	60	100.0%	40	100.0%	

Note: p value* significant at 5% level of significance ($p < 0.05$) 20% of the epileptic children on AEDs were having below normal serum calcium level while serum calcium level in healthy control is normal. This difference is statistically significant.

Table 6: Sr. Phosphorus Levels Between Cases And Controls

Sr.Phosphorus (mg/dl)	EC group		Controls		p value
	N	%	N	%	
Below the normal	11	18.3%	0	0.0%	0.004*
Normal	49	81.7%	40	100.0%	
Total	60	100.0%	40	100.0%	

Note: p value* significant at 5% level of significance ($p < 0.05$) 18.3% of the epileptic children on AEDs were having below normal serum phosphorus level while serum phosphorus level in healthy control is normal. This difference is statistically significant.

Table 7: Sr. Alkaline Phosphatase Levels By Cases And Controls

Sr. Alkaline Phosphatase (mg/dl)	EC group		Controls		p value
	N	%	N	%	
Normal	42	70.0%	40	100.0%	<0.001*
Raised	18	30.0%	0	0.0%	
Total	60	100.0%	40	100.0%	

Note: p value* significant at 5% level of significance (p<0.05) 30% of the epileptic children on AEDs were having above normal serum alkaline phosphatase level for age while serum alkaline phosphatase level in healthy control is normal for age. This difference is statistically significant.

Table 8 : Vitamin D levels between Cases and Controls

Vitamin D (ng/ml)	EC group		Controls		p value
	N	%	N	%	
Below the normal	12	20.0%	0	0.0%	0.003*
Normal	48	80.0%	40	100.0%	
Total	60	100.0%	40	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

20% of the epileptic children on AEDs were having below normal vitamin D level while vitamin D level in healthy control is normal.

-This difference is statistically significant.

Table 9: BMD levels by DXA scan between Cases and Controls

DXA Scan	EC group		Controls		p value
	N	%	N	%	
Lower than normal limit	8	13.3%	0	0.0%	0.016*
Normal	52	86.7%	40	100.0%	
Total	60	100.0%	40	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

13.3% of the epileptic children on AEDs were having below normal bone mineral density level (DEXA scan showing lower than normal limits) while bone mineral density in healthy control is normal. This difference is statistically significant.

Table 10: Sr. Calcium levels between Monotherapy and Polytherapy groups

Sr. Calcium (mg/dl)	Mono therapy		Poly therapy		p value
	N	%	N	%	
Below the normal	4	9.5%	8	44.4%	0.002*
Normal	38	90.5%	10	55.6%	
Total	42	100.0%	18	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

44.4% of the cases on poly therapy showed below normal serum calcium level compared to 9.5% cases on mono therapy showed below normal serum calcium level. This difference is statistically significant.

Table 11: Sr. Phosphorus levels between Monotherapy and Polytherapy groups

Sr.Phosphorus (mg/dl)	Mono therapy		Poly therapy		p value
	N	%	N	%	
Below the normal	3	7.1%	8	44.4%	0.001*
Normal	39	92.9%	10	55.6%	
Total	42	100.0%	18	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

44.4% of the cases on poly therapy showed below normal serum phosphorus level compared to 7.1% cases on mono therapy showed below normal serum phosphorus level. This difference is statistically significant.

Table 12: Sr. Alkaline phosphatase levels between Monotherapy and Polytherapy groups

Sr. Alkaline Phosphatase (mg/dl)	Mono therapy		Poly therapy		p value
	N	%	N	%	
Normal	34	81.0%	8	44.4%	0.005*
Raised	8	19.0%	10	55.6%	
Total	42	100.0%	18	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

55.6% of the cases on poly therapy showed above normal serum alkaline phosphatase level for age compared to 19.0% cases on mono therapy showed above normal serum alkaline phosphatase level for age. This difference is statistically significant.

Table 13: Vitamin D levels between Monotherapy and Polytherapy groups

Vitamin D (ng/ml)	Mono therapy		Poly therapy		p value
	N	%	N	%	
Below the normal	4	9.5%	8	44.4%	0.002*
Normal	38	90.5%	10	55.6%	
Total	42	100.0%	18	100.0%	

Note: p value* significant at 5% level of significance (p<0.05) 44.4% of the cases on poly therapy showed below normal Vitamin D level compared to 9.5% cases on mono therapy showed below normal Vitamin D level.

This difference is statistically significant.

Table 14: BMD level by DEXA scan between Monotherapy and Polytherapy groups

DXA Scan	Mono therapy		Poly therapy		p value
	N	%	N	%	
Lower than normal limit	2	4.8%	6	33.3%	0.003*
Normal	40	95.2%	12	66.7%	
Total	42	100.0%	18	100.0%	

Note: p value* significant at 5% level of significance (p<0.05)

33.3% of the cases on poly therapy showed below normal bone mineral density level compared to 4.8% cases on mono therapy showed below normal bone mineral density level.

This difference is statistically significant.

Table 15: Correlation between Duration of AEDs with Biochemical parameters

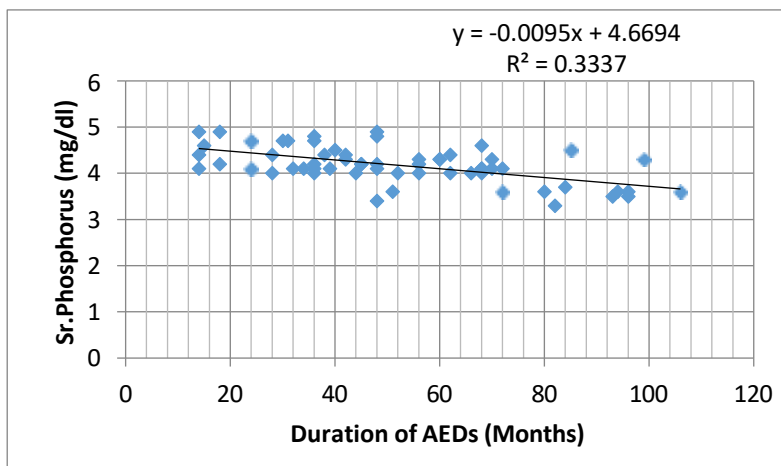
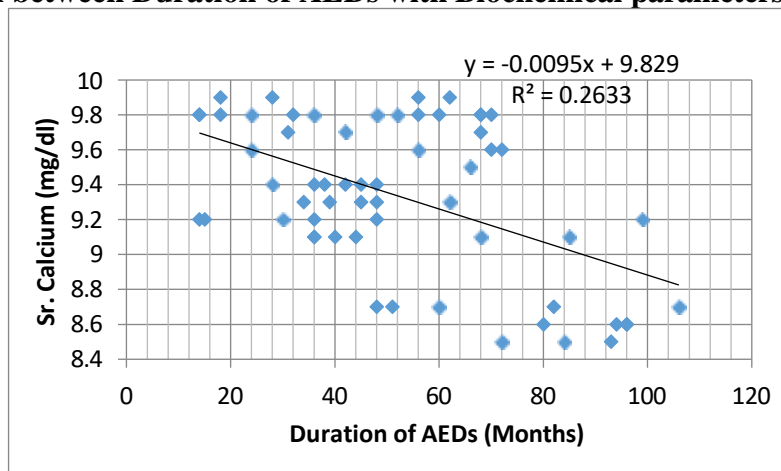
Correlation of Duration of AEDs with BMD parameters	r value	p value
Sr. Calcium (mg/dl)	-0.513	<0.001*
Sr.Phosphorus (mg/dl)	-0.578	<0.001*
Sr. Alkaline Phosphatase (mg/dl)	0.430	0.001*
Vitamin D (ng/ml)	-0.432	0.001*

Note: p value* significant at 5% level of significance (p<0.05)

Longer duration of the treatment showed lower values of serum calcium, serum phosphorus, vitamin D levels and higher serum alkaline phosphatase levels for age in cases.

This value is statistically significant.

Figure 1: Correlation between Duration of AEDs with Biochemical parameters



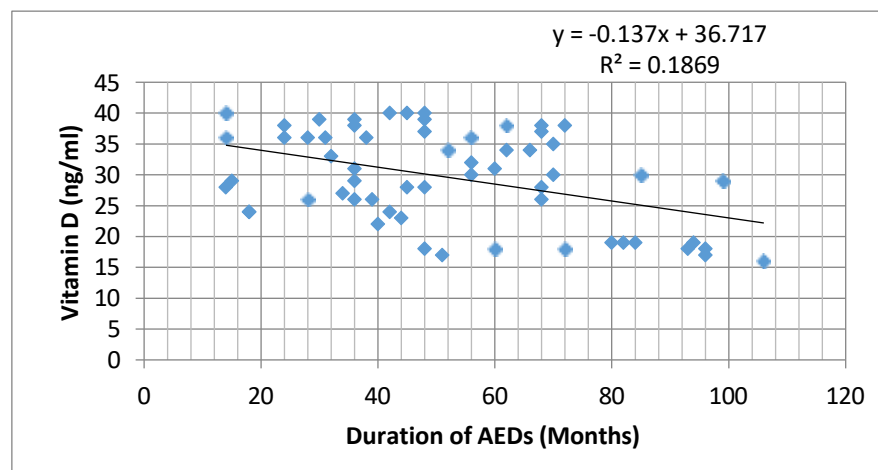
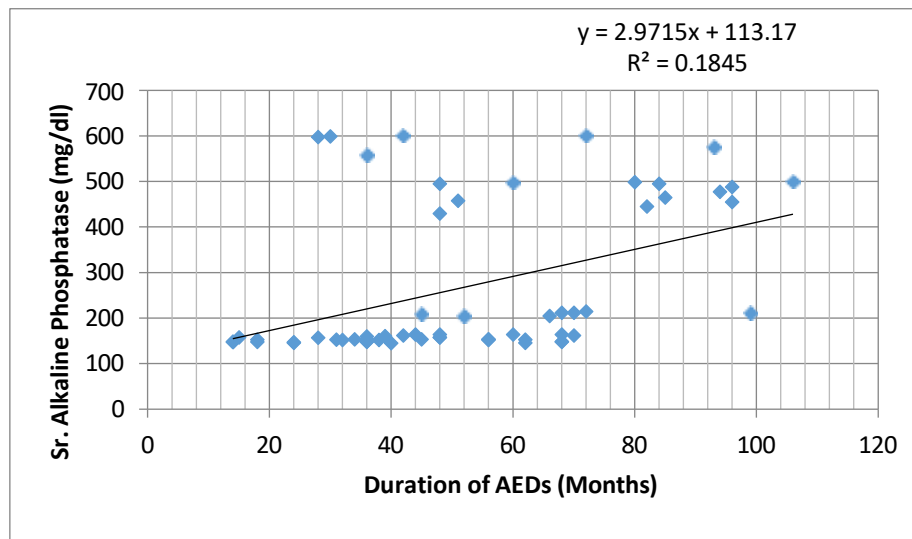


Table 16: Association between Duration of AEDs with BMD by DXA Scan

Parameters	DXA Scan				p value
	Lower than normal limit		Normal		
	Mean	SD	Mean	SD	
Duration of AEDs (Months)	82.0	21.4	26.9	28.5	<0.001*

Note: p value* significant at 5% level of significance ($p < 0.05$)

Cases with lower BMD on DEXA scan had mean duration of therapy of 82 months with SD of 21.4 compared to cases with normal BMD on DEXA scan had mean duration of therapy of 26.9 months with SD of 28.5. This difference is statistically significant.

DISCUSSION

In our study, the cases and controls were taken randomly and we found that maximum number of the cases will fall under the age group of 6-10 years. A study conducted by Bothina Hasaneen et al, in 152 participants 70 children were from similar age group. [12]

In our study, all 40 healthy controls have normal serum calcium level while in 60 epileptic children, 12 cases(20%), sr. calcium level is lower than normal value. Similar results found in a study by Bothina Hasaneen et al, [12] found that the serum level of calcium was significantly low ($P > 0.05$) in total epileptic

cases on AEDs versus control. A study done by Ebtasam Mohamed Fahmy et al, [13] concluded that Serum calcium was significantly lower in epileptic patients compared to control subjects.

In our study, all 40 healthy controls showed normal serum phosphorus level while 11 (18.3%) cases showed lower serum phosphorus value. Similar results found in a study conducted by Bothina Hasaneen et al, [12] that the serum level of phosphorus was significantly low ($P > 0.05$) in epileptic children on AEDs versus control. A study done by Ebtasam Mohamed Fahmy et al, [13] concluded that serum phosphorus was significantly lower in epileptic patients compared to control subjects.

In our study, all 40 healthy controls showed normal serum alkaline phosphatase level for age while 18 (30%) cases showed higher serum alkaline phosphatase value for age. Similar results found in a study done by Bothina Hasaneen et al,[12] that the serum level of serum alkaline phosphatase significantly high ($P > 0.05$) in total epileptic children on AEDs versus control. A study done by Ebtasam Mohamed Fahmy et al, [13] concluded that Serum alkaline phosphatase was significantly higher in epileptic patients compared to control subjects. A study done by ArzuBabayigit MD et al, [14] concluded that serum alkaline phosphatase concentrations were higher in epileptic children on AEDs as compared with the control subjects.

In our study, 44.4% epileptic children on polytherapy had lower Vitamin D level compared to 9.5% epileptic children on monotherapy. Similar results found in An observational prospective controlled cohort study, done by Bothina Hasaneen et al, In this study, found that the serum level of Vitamin D significantly low($P > 0.05$) in epileptic children on polytherapy versus monotherapy.

In our study, 33.3% epileptic children on polytherapy had lower bone mineral density level compared to 4.8% epileptic children on monotherapy. Similar results found in an observational prospective controlled cohort study, done by Bothina Hasaneen et al[12], In this study, found that bone mineral density done by DEXA scan was significantly low($P > 0.05$) in epileptic children on polytherapy versus monotherapy. A study done by ArzuBabayigitMD, et al, [14] concluded that serum alkaline phosphatase concentrations were higher in the patient group on polytherapy with valproic acid, carbamazepine, or with oxcarbazepine as compared with the control subjects.

In our study, as duration of AEDs increased, Sr. Calcium, Sr. Phosphorus and Vitamin D levels were lower and Sr. Alkaline phosphatase levels were higher. In our study, as duration of AEDs increased, bone mineral density values(DEXA scan-lower than normal limit) were lower. Similar results found in an observational prospective controlled cohort study done by Bothina Hasaneen et al[12], found that the serum level of calcium and phosphate were significantly low ($P > 0.05$) , serum alkaline phosphatase and PTH were significantly high ($P > 0.05$) and there was a significant decrease of BMD and Z-score for the total body and lumbar area in the total cases versus control ($P > 0.05$)in epileptic children on AEDs for longer duration versus controls.

A study done by Ebtasam Mohamed Fahmy et al, [13] concluded that Serum calcium, phosphorus, and vitamin D were significantly lower, whereas serum and alkaline phosphatase was significantly higher in epileptic patients compared to control subjects. Bone mineral density (BMD) abnormalities were detected in 22 patients (73.4%) in case of epileptic children on AEDs for longer duration.

CONCLUSION

The most often used AED is sodium valproate, which is followed by levetiracetam. Children with epilepsy on AEDs had much reduced blood levels of calcium, phosphorus, and vitamin D. Children with epilepsy who are on AEDs have a noticeably elevated serum alkaline phosphatase level. Children with epilepsy on AEDs had a considerably decreased BMD by DEXA scan. Compared to children receiving polytherapy, epileptic

children receiving polytherapy have substantially reduced BMD by DEXA scan. When children with epilepsy get long-term anti-epileptic treatment, their blood levels of calcium, phosphorus, and vitamin D are considerably reduced. Children with epilepsy who get long-term anti-epileptic treatment have a noticeably elevated serum alkaline phosphatase level. Children with epilepsy who get long-term anti-epileptic treatment have a considerably reduced BMD by DEXA scan.

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