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To determine the effect of variables of antiepileptic therapy on bone mineral density in children with idiopathic epilepsy

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Abstract

Introduction: Epilepsy is a major public health concern affecting nearly 50 million people worldwide and antiepileptic therapy is generally chronic and mostly lifelong. Many factors can hinder this active mineralization which results in weakening of bone. Chronic illness, particularly renal disease and other diseases adversely affects the mineralization process. Reduction of bone mineralization has been shown to result in increased bone fragility and thereby chance for future fractures.

Objectives: We aimed to determine effect of variables of antiepileptic therapy on bone mineral density in children with idiopathic epilepsy.

Methodology: This was a cross sectional study carried out at SPMC, Bikaner, Rajasthan from 2020 - 2021.Around 150 epileptic patients who were on AED therapy for more than 6 months participated in this study, all cases underwent bone mineral density estimation by the latest DEXA scan BMTECH osteopro

Results: Children on multiple AEDs, enzyme inducing antiepileptic drugs and with more than 2 years duration of drug therapy had significantly lower mean BMI, LSBMD, LSBMAD. Phenytoin and Levetiracetam were associated with maximum bone loss in our study. Factors having significant strong negative correlation with LSBMAD were number of AEDs, duration of AEDs, weight, height and bone area with p value <0.001

Conclusion: Low bone mineral was significantly related to duration of therapy, use of multiple drugs and enzyme inducer AEDs. The present study underscores the importance of variables of antiepileptic therapy on bone health and also judicious selection of AEDs.

Keywords: AED therapy, BMD, DEXA scan, Epilepsy, Inducers, Leveteracetam, polytherapy, Phenytoin, Sodium valproate

Introduction

Epilepsy is a major public health concern affecting nearly 50 million people worldwide and antiepileptic therapy is generally chronic and mostly life long, Epilepsy is a disorder of the brain which is characterized by an enduring predisposition to evoke seizures and by its cognitive, neurobiological, psychological, and social consequences[1][2].The International League Against Epilepsy (ILAE) published the most recent classification of epilepsies and seizures in March 2017[3][4].The clinical features of epilepsy are categorized into three levels: the seizures, the epilepsies, and the epilepsy syndromes in this current classification by ILAE[5][6].

Bone is metabolically active to a high degree, as it receives 10% of cardiac output. Many factors can hinder this active mineralization which results in weakening of bone. Reduction of bone mineralization has been shown to result in increased bone fragility and thereby chance for future fractures [7]. Any interruption with mineralization process will result in attainment of a lower peak bone mass during childhood and adolescence. Chronic illness, particularly renal disease and other diseases adversely affects the mineralization process as it impairs constitutional development. Furthermore, most of the drugs used in the treatment of chronic disease also adversely affect bone mineralization

Among the medications, long-term corticosteroid treatment exerts the most adverse influence in bone. There is increasing evidence suggesting that epilepsy and its treatment, or conditions comorbid with epilepsy, such as cerebral palsy and the hypo motor state can also adversely affect bone mineralization in childhood and adolescence. Any condition or treatment that adversely affects bone mineralization, results in a lower peak and plateau of bone density, and thus patient may enter into the years of bone involution with less bone reserve, thereby lowers the fracture threshold. A lower peak bone mass attained at the end of adolescence is associated with greater involutional osteoporosis and risk for fracture in the elderly [9]. Peak bone mineral density is influenced by many factors like genetic, hormonal, and exogenous factors. Exogenous factors that exert a negative impact on peak bone mineral density includes cigarette smoking, physical handicaps, poor calcium intake and certain medications used for chronic diseases like steroids and AEDs [8]. From various studies it is evident that phenytoin, primidone, and phenobarbital contribute to osteomalacia and rickets [10].

This study was designed to determine the effect of variables of antiepileptic therapy on bone mineral density in pediatric epileptic children in the age group 5 to 15 years in North western India.

Materials and methods

This study was conducted in pediatric hospital in Sardar Patel Medical college Bikaner from December 2020-November 2021. Bone mineral density was evaluated using bone densitometer (OSTEOPRO DEXA by BM TECH), Osteopro is a pencil beam type of DEXA bone densitometer. Child's lumbar spine (LV1-LV4) was examined in supine position with their lower limbs partially raised to reduce lumbar lordosis. To reduce the effect of growth and bone size on bone mineral density, we calculated the bone density per unit volume [19][20]. Hence, bone mineral apparent density (BMAD) in lumbar area was calculated trough the following formula,

$$\text{Lumbar BMAD} = \frac{\text{BMC of L2–L4}}{\text{Bone area}^{1.5}}$$

Study design

This was an observational cross-sectional study. The prevalence of children having reduced bone mineral

density with use of antiepileptics ranges from 20-85% from previous studies [26]. Taking an average prevalence of 40% for this study the sample size was calculated to be 150 using the formula,

$$n = \frac{z^2 \, p \times q}{d^2}$$

150 children between 5 to 15 years having epilepsy defined by having at least two unprovoked seizures more than 24 hour apart and who were are on antiepileptic drugs for longer than six months duration were included in our study. Children with ddiseases primarily involving bone metabolism such as Rickets & hypoparathyroidism or familial history of bone metabolism disorder like renal failure, liver diseases & those who were on cchronic treatment with drugs other than anticonvulsants were excluded from our study.

Statistics

150 children with AED therapy more than 6 months who were diagnosed cases of epilepsy participated in this study All the parents or guardians, signed a written informed consent.

The collected data was coded, tabulated and statistically analysed using SPSS software (statistical package for social science) version 26. Descriptive statistics for numerical data by mean, standard deviation and minimum and maximum of the range. Analysis will be done for parametric quantitative data between the two groups using independent sample t test.

The standard deviation and the distance from mean to limit values were assumed based on the previous published normal BMD reference [11]. The mean and standard deviation (SD) of BMD of the LS (LSBMD), LSBMAD and BA of the LS were calculated for each age group in boys and girls. The unpaired t-test was used to determine differences in these parameters between boys and girls of the same age group. The best models for the relationships between age vs LSBMD, LSBMAD and BALS were chosen by regression analysis.

Student's t test and Mann–Whitney test were used to compare quantitative data whereas Chi square test and fisher exact test were used to compare qualitative data in two groups. Analysis of covariance (ANCOVA) was used to compare each DEXA outputs between cases and controls. Binary logistic regression was used to compare prevalence of low bone mass in lumbar, considering serum vitamin D level. Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed. P value of < 0.05 was considered to be statistically significant.

Results

The mean age of cases was 9.94 ± 2.61. Majority of children in the study group were in the age group between 9-11 years followed by age group 11-13. 63.3 % were males and 36.7 % were females in our study. Out of 150 patients, 93 (62.0%) were receiving monotherapy and the rest 57 (38.0%) were on polytherapy. Only 18 patients (12%) were on enzyme inducer group of drugs. The mean duration of AED therapy in our study was 18.63 ± 10.55 months. In the study group, 87 out of 150 subjects (58 %) were on antiepileptic therapy for less than 2 years and around 42 % of subjects took antiepileptic therapy for more than 2 years. Children on multiple AEDs, enzyme inducing antiepileptic drugs and with more than 2 years duration of drug therapy had significantly lower mean BMI, LSBMD and LSBMAD levels with p value <0.001 as compared to those who were on monotherapy, non-enzyme inducer group of AEDs and less than 2 years of drug therapy (Table 1,2,3).

Gender based differences amongst study group males and females for LSBMD and LSBMAD were not statistically significant (Table 4). Factors having significant strong negative correlation with LSBMAD were number of AEDs, duration of AEDs, weight, height and bone area with p value <0.001 (Table 5). There was a weak negative correlation between Number of AEDs and LSBMAD (g/cm²), and this correlation was statistically significant (rho = -0.29, p = <0.001). that implies for every 1 unit increase in Number of AEDs, the LSBMAD (g/cm²) decreases by 0.06 units (diagram 6) while there was a moderate negative correlation between Duration of AEDs (Months) and LSBMAD (g/cm²), and this correlation was statistically significant (rho = -0.44, p = <0.001). that means for every 1 unit increase in Duration of AEDs (Months), the LSBMAD (g/cm²) decreases by 0.01 units (diagram 7)

Phenytoin and Leveteracetam were assosiated with maximum bone loss. The variable LSBMAD (g/cm²) was normally distributed in the 2 subgroups of the variable Ongoing AEDs: L. Thus, parametric tests (t-test) were used to make group comparisons.

There was a significant difference between the 2 groups in terms of LSBMAD (g/cm²) (t = -2.538, p = 0.016), with the mean LSBMAD (g/cm²) being lowest in those who were on Leveteracetam. (Table 8)

The variable LSBMAD (g/cm²) was not normally distributed in the 2 subgroups of the variable Ongoing Phenytoin. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. There was a significant difference between the 2 groups in terms of LSBMAD (g/cm²) (W = 646.000, p = 0.010), with the mean LSBMAD (g/cm²) being lowest in those receiving phenytoin. (Figure 9)

Discussion

Enzyme inducer group of AED's like phenytoin, primidone phenobarbital and carbamazepine were most commonly associated with the drug induced bone disorders as they induce enzymes of the cytochrome p 450. In a study by Nasr Mohamed M. Osman et al[14] the Mean age of study group was 9.03 ± 2.02 & out of 60 subjects 38 were males (63.3%) and 22 were females (36.7%) this was also similar to our study .In our study, the mean LSBMAD in the polytherapy group was lower than that of monotherapy group with P = 0.001 this was similar to study done by Guo et al[15],Vestergaardet al[16] and Coppola et al[17] while in contrast Farhat et al[18] found out that there was no reduction in bone mineral density.in polytherapy group.

Petty SJ et.al [19] studied patients using antiepileptics for 2 years or more and found out that they had a significant lower bone mineral density at clinically relevant fracture risk sites. On the other side Nasr Mohamed M. Osman et al [14] in 2017 revealed that epileptic patients receiving polytherapy showed more decrease in BMD than that of epileptic patients receiving monotherapy with (P < .001). Also, Pati cheep et al [20] reported that polytherapy of antiepileptic drugs and duration of antiepileptic drug administration correlate with low bone mineral density

Sato et al [21] studied 40 subjects receiving valproate monotherapy on which, 23% had osteoporosis and 37% had osteopenia. The investigators also found an inverse relationship between duration of valproate therapy and bone density. This effect was present despite increased weight, which is typically associated with a protective effect on bone mineralization

In our study patients receiving enzyme inducers had a lower LSBMD and LSBMAD when compared with non-enzyme inducing AEDs furthermore it was statistically

significant with p value ($p < 0.05$). Cross-sectional studies done by Hahn TJ et.al [22] in children with intractable symptomatic epilepsy have shown that around 50% of those treated with the classic AEDs such as phenobarbital, primidone, and phenytoin showed changes in serum markers that were suggestive of osteomalacia. Farhat et al [18] in a cohort study reported that patients taking non-enzyme inducing AEDs had a lower total body bone mineral content compared to those taking enzyme-inducing AEDs, although this difference did not reach statistical significance.

In accordance with our study, Salim pour et al [23] and Meier et al [24] found a significant difference in BMD and bone metabolism between children treated with AEDs and healthy controls showing a significant reduction in bone mineral density (BMD) and an increased fracture risk in patients treated with enzyme-inducing antiepileptic (phenobarbital, carbamazepine, phenytoin).

Significantly lower values of mean LSBMD and LSBMAD were observed in both male and female epileptic patients as compared to their healthy control groups. The mean LSBMAD was significantly lower in males but in females it was not significantly low. Gender based differences amongst study group males and females for LSBMD and LSBMAD were not statistically significant. This was in contrast with the study done by Kafali et al [25] who found out a 4.5% reduction in bone density pronounced in girls than in boys which was not statistically significant.

The limitation of our study were a) Single cantered hospital based observational study b) Small sample size for individual AEDs like carbamazepine, phenytoin and newer AEDs and also effect of dose of AEDs not correlated c) Tanner staging was not taken into consideration

Conclusion

Low bone mineral density was observed in all age groups who were on antiepileptic therapy but it was more pronounced in the adolescents and was significantly related to duration of therapy, use of multiple drugs and enzyme inducer AEDs. The present study highlights the importance of judicious selection of AEDs and will stimulate a high index of suspicion to facilitate early diagnosis.

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"What is Already known"

We already knows that antiepileptic drugs are associated with bone loss in adults and elderly people and mainly by enzyme inducer group of AEDs like phenytoin phenobarbitone and carbamazepine. The effect of AEDs in pediatric bone health datas are meagre in literature.

"What This Study Adds"

Our study confirms the facts what we know about AEDs that it also affects pediatric bone health. The bone loss is more evident in adolescent age groups and the intensity of bone loss is directly proportional to duration of therapy, number of drugs and enzyme inducer group of drugs. Phenytoin and Levetiracetam were associated with maximum bone loss in our study.

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Legend Tables and Figures

Variables	Mono therapy (N=93)	Poly therapy (N=57)	p value
BMI (kg/m^2) ***	16.04 ± 2.35	14.93 ± 2.69	0.002[1]
LSBMD (g/cm^2) ***	0.51 ± 0.05	0.47 ± 0.06	<0.001[1]
LSBMAD***	0.49 ± 0.13	0.42 ± 0.13	0.001[1]

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test,

Table no 1: Clinical characteristics and bone mineral density (BMD) in patients on single and multiple therapy

Parameters	Duration of therapy (years)		
	<2 years	> 2 years	P value
BMI (Kg/m²) ***	17.2 ± 5.25	13.5 ± 4.87	0.03
LSBMD (g/cm²)	0.5 ± 0.13	0.4 ± 0.13	0.07
LSBMAD (g/cm²) ***	0.46 ± 0.09	0.38 ± 0.14	0.04

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Fisher's Exact Test, 4: t-test

Table no 2: Bone mineral status in patients on the basis of duration of antiepileptic therapy

Parameters	Enzyme inducer N= 18	Non-enzyme inducer N= 132	P value
BMI (Kg/m²) ***	13.98 ± 2.05	15.85 ± 2.51	0.001[1]
LSBMD (g/cm²) ***	0.44 ± 0.06	0.50 ± 0.05	<0.001[1]
LSBMAD (g/cm²) ***	0.39 ± 0.14	0.48 ± 0.13	0.006[1]

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Fisher's Exact Test, 4: t-test

Table no 3 Comparison between Enzyme inducers and non-Enzyme inducers on bone status in study group

Parameters	Study group males (N= 95)	Study group Girls (N=55)	P value
BMI (Kg/m²)	15.85 ± 2.58	15.22 ± 2.42	0.086[1]
LSBMD (g/cm²)	0.49 ± 0.06	0.49 ± 0.05	0.231[1]
LSBMAD (g/cm²)	0.46 ± 0.14	0.47 ± 0.13	0.052[1]

***Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Fisher's Exact Test, 4: t-test

Table no 4: Gender based difference in various parameters in study group

Parameters	LSBMAD (g/cm²)	p value
Number of AEDs***	Correlation Coefficient (rho) = - 0.29	<0.001[1]
AED Number***		0.001[3]
Monotherapy	0.49	
Polytherapy	0.42	

Parameters	LSBMAD (g/cm²)	p value
Duration Of AEDs (Months)***	Correlation Coefficient (rho) = - 0.44	<0.001[1]

***Significant at p<0.05, 1: Spearman Correlation, 2: Kruskal Wallis Test, 3: Wilcoxon-Mann-Whitney U Test

Table 5: Association between LSBMAD (g/cm²) and Parameters

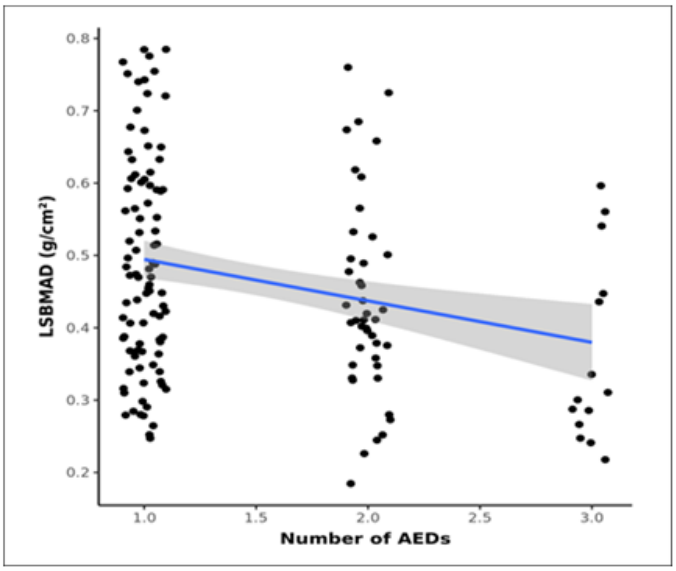

Figure 1: Correlation between Number of AEDs and LSBMAD (g/cm²) (n = 150)

The above scatterplot depicts the correlation between Number of AEDs and LSBMAD (g/cm²). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

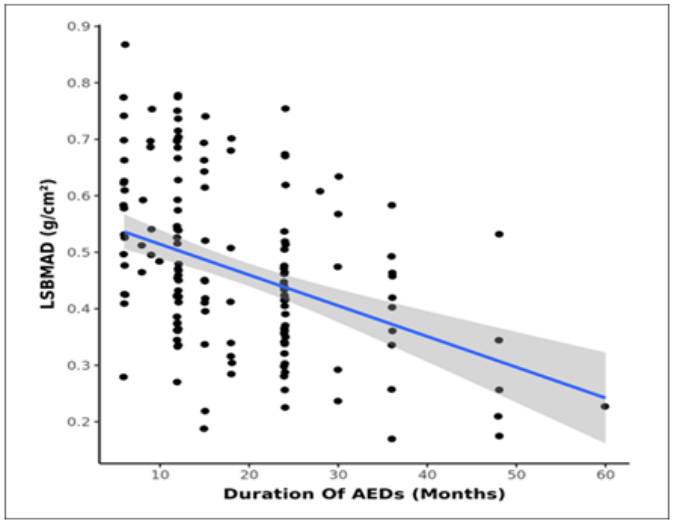

Figure 2: Correlation between Duration of AEDs (Months) and LSBMAD (n = 150)

The above scatterplot depicts the correlation between Duration of AEDs (Months) and LSBMAD (g/cm²). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

LSBMAD (g/cm²)	Ongoing AEDs: L		t-test	
	Yes	No	t	p value
Mean (SD)	0.41 (0.12)	0.50 (0.13)	-2.538	0.016
Median (IQR)	0.38 (0.34-0.47)	0.49 (0.41-0.59)		
Range	0.26 - 0.67	0.27 - 0.77		

Table 6: Comparison of the 2 Subgroups of the Variable Ongoing Leveteracetam in Terms of LSBMAD (g/cm²)

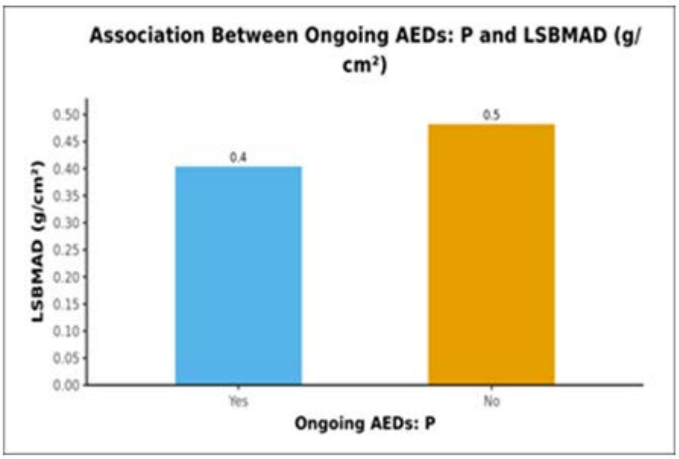

Figure 3: The bar graph below depicts the means of LSBMAD (g/cm²) in the 2 different groups. With ongoing Phenytoin and those who were not on phenytoin