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Original Article

ASSESSMENT OF OSTEOPOROSIS AND ANAEMIA RISK IN PATIENTS ON ANTICONVULSANT THERAPY

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ABSTRACT

Objective: To assess the incidence of osteoporosis and anaemia in patients on anticonvulsant therapy and to educate those under risk.

Methods: A prospective observational study was conducted on 50 study participants. The Bone mineral density (BMD), vitamin D, hematological parameters and peripheral smear were noted. Data analyzed using different statistical methods. Patient information brochures for osteoporosis and anaemia were distributed to those on chronic anti-epileptic drug (AED) therapy.

Results: The prevalence of osteoporosis was 16% and osteopenia 22%. The BMD of subjects showed an Insignificant reduction in BMD when compared with a standard reference value for south asian population (*P>0.05). The mean BMD in single therapy group was higher compared with multiple therapy groups. BMD of the enzyme-inducing class was less compared with non-enzyme inducing class but was not significant (P>0.05). Duration of therapy was compared with BMD of patients showed a negative correlation. The relationship between duration of therapy and hematological parameters showed a negative correlation (r =-0.128). The mean haematological parameters in single AED therapy were higher when compared with multiple AED therapy. The study demonstrated 40% microcytic hypochromic and 4% macrocytic hypochromic morphology.

Conclusion: Chronic therapy with AEDs possesses a significant risk of developing osteoporosis and anaemia. The incidence rate varies according to the type, duration, and mode of therapy. Early detection and management through diet exercise or pharmacotherapy will decrease the incidence of unwanted effects due to AEDs and improve the quality of life.

Keywords: Bone mineral density, Antiepileptic drug, Osteoporosis

INTRODUCTION

Epilepsy is defined as a chronic seizure disorder or group of disorders characterized by seizures that usually recur unpredictably in the absence of a consistent provoking factor. The incidence of osteoporosis increases after the age of 60. Treatment with older antiepileptic such as phenytoin, carbamazepine and phenobarbital has been associated with the production of rickets and osteoporosis and could theoretically contribute to bone demineralization. Early reports suggest that 20-65% of epileptic patients receiving anticonvulsant develop signs of osteoporosis. Chronic therapy with the anti-epileptic drug (AED) causes abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated levels of serum alkaline phosphatase and serum parathyroid hormone, reduced serum levels of biologically active vitamin D metabolites, radiologic evidence of rickets, and histological evidence of osteomalacia. The mechanism of these abnormalities remains unclear [1]. Similarly, anaemia is one of the complications associated with antiepileptic therapy characterized by decreased red blood cell (RBC) and haemoglobin levels. Drugs such as carbamazepine and phenytoin were suspected to be associated with increased risk of agranulocytosis and aplastic anaemia; also drugs such as primidone, barbiturates, phenytoin either alone or in combination can cause megaloblastic anaemia, the precise mechanism of anaemia development remains uncertain [2]. Hence, the objective of the study was to determine the risk of occurrence of osteoporosis and anaemia with AED therapy and to provide patient education for those identified under risk for the same.

MATERIALS AND METHODS

Study design

This prospective observational study evaluated the effect of long-term AED therapy on bone density and haematological parameters in a group of epileptic patients who presented to our hospital between January 2015 to June 2015. The study was approved by the Institutional human ethics committee (Ref: 15/019) and informed consent was obtained from all patients.

Subjects

Fifty epileptic patients, both male and female aged above 18 y on chronic AED therapy for at least six months were enrolled in the study. Patients with conditions known to affect bone metabolism and haematological parameters such as hepatic and renal disorders, hypothyroidism, malabsorption, history of anemia, diabetes mellitus, medications that affect bone turnover (vitamin A,steroids, gluco-corticoids, thiazides, calcitonin, bisphosphonates), pregnant and breastfeeding women were excluded from the study.

Study tools

Bone mineral density (BMD)

The BMD of lumbar spine and hip were evaluated using a Lunar Prodigy DXA densitometer. BMD reference values for males and females of south Asian population were obtained [3].

	BMD	Standard deviation
Males		
Spine	0.967 g/cm^2	0.0109 g/cm^2
Hip	0.880 g/cm^2	0.0108 g/cm^2
Females		
Spine	0.932 g/cm^2	0.0109 g/cm^2
Hip	0.808 g/cm^2	0.0116 g/cm^2

T-score was estimated using the formula

$$T\text{-}score = \frac{(BMD)subject - (BMD)reference}{(SD)reference}$$

In adults, osteopenia and osteoporosis were determined according to the World Health Organisation's (WHO) operational definition for these terms. Osteoporosis was defined as BMD T-score at any site less than-2.5 and osteopenia was defined as BMD T-score between-1 and-2.5.

Vitamin D levels

Serum 25–hydroxy (OH) vitamin D were measured using Radioimmunological assay. Patients with 25–OH vitamin D level less than 20 ng/ml were regarded as having vitamin D deficiency [13].

Anaemia

In adults, anaemic status was determined using haemoglobin (Hb) levels according to the WHO's operational definition for these terms. Also packed cell volume (PCV), RBC count and peripheral smear were obtained.

Classification of AED according to their enzyme inducing effect

The enzyme-inducing AEDs in our study were phenytoin, carbamazepine, oxcarbazepine and primidone. The non-enzyme inducing AEDs were levetiracetam, valproic acid, lamotrigine, gabapentin, clobazam, ethosuximide, lacosamide and zonisamide. For patients receiving more than one AED if any of the drugs was an enzyme inducer drug, the patient was included in the enzyme-inducing group.

Statistical analysis

The analysis was made using SPSS version 20 software. Comparisons of continuous variables between various subgroups were performed using two–tailed t-test.

Association between outcome variables and covariates was examined using bivariate analysis (Pearson's correlation, multiple regression models and Student t–test). Significance was established at *P<0.05.

Table 1: WHO definition for classification of anaemia

	Absent (g %)	Mild (g %)	Moderate (g %)	Severe (g %)
Non pregnant women (>15yrs)	12 or greater	11–11.9	8–10.9	Less than 8
Men	13 or greater	11–12.9	8–10.9	Less than 8

RESULTS

Clinical characteristics of the study groups

Baseline demographic and clinical characteristics of study subjects are provided in table 2. Among the fifty participants, 27 were males and 23 were females with a mean duration of therapy 32.16±32.17 mo. The mean vitamin D level was 17.51±4.76 ng/ml Fifty-four percentages of patients were on enzyme-inducing drugs, and forty-six percentages were on enzyme-inducing drugs. In the study, the prevalence of osteoporosis in epileptic patients was determined to be 16% and osteopenia was 22% represented in fig. 1. 20% had mild and moderate anaemia and 4% had severe anaemia showed in fig. 2.

Table 2: Baseline characteristics

Variables	Values
Age *	39.24±18.92
Sex	
Male/Female	27/23
Duration of therapy (months)*	32.16±32.17
Vitamin D level (ng/ml)*	17.51±4.76
Type of therapy (n %)	
Enzyme inducers	54%
Non–enzyme inducers	46%
Mode of therapy (n %)	
Single	20%
Multiple	80%
Bone health (n %)	
Osteoporosis (spine/hip)	16%
Osteopenia (spine/hip)	22%
Haematological parameters*	
RBC	4.6±0.69 x 10^6/µl
Haemoglobin	12.49±2.13 g/dl
PCV	38.67±4.57 %
Anaemia (n %)	
Mild	20%
Moderate	20%
Severe	4%

*Values are expressed as mean±standard deviation (SD)

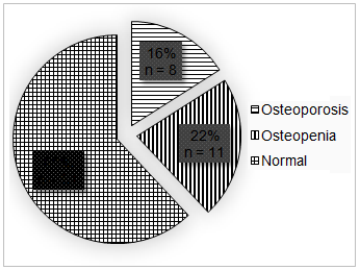

Fig. 1: Prevalence of osteoporosis and osteopenia

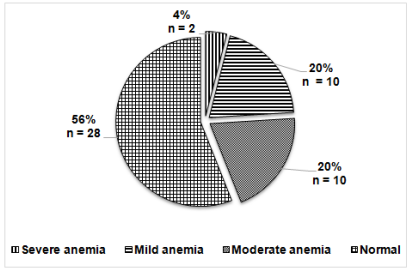

Fig. 2: Prevalence of mild, moderate and severe anaemia

Relationship between Vitamin D and BMD

Out of the total study population, 76% had vitamin D deficiency (<20 ng/ml). Their BMD values were in positive correlation with serum 25-OH vitamin D values which are represented in fig. 3 and 4.

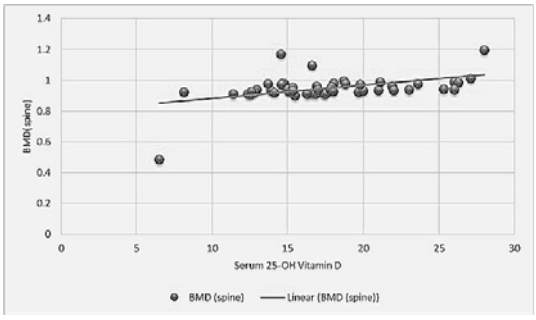

Fig. 3: Correlation between 25-OH vitamin D and BMD (spine)

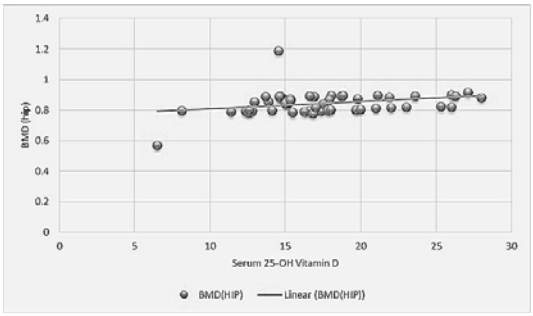

Fig. 4: Correlation between 25-OH vitamin D and BMD (hip)

BMD

The mean BMD of study subjects is provided in table 3. The mean BMD of lumbar spine and hip was less than the reference values used, but the differences were not statistically significant (*P>0.05).

Table 3: Baseline BMD

Site of bone mass	Values
Lumbar spine (g/cm^2)	0.948±0.088
T-score	-0.570±1.872
Hip (g/cm^2)	0.843±0.075
T-score	-0.483±1.539

Values are expressed as mean±SD

Impact of type/mode of AED on Vitamin D level and BMD

Enzyme-inducing and non-enzyme inducing therapy

BMD of the enzyme-inducing class was less compared with the non-enzyme inducing class which was analyzed using independent two-tailed T-test (P>0.05), but was not statistically significant represented in table 4. The mean vitamin D level in the enzyme-inducing group was greater than the non-enzyme inducing group, but the differences were not statistically significant (P>0.05).

Single vs. multiple AED therapy

The mean BMD (spine and hip) in single therapy group was higher compared with multiple therapy groups, but the difference was not statistically significant (P>0.05) shown in table 5.

Impact of type/mode of AED on hematological parameters

Enzyme-inducing and non-enzyme inducing therapy

The mean RBC count, Hb and PCV in enzyme-inducing AED therapy was higher when compared with non-enzyme inducing AED therapy, but it was not statistically significant represented in table 6.

Table 4: Serum 25-OH vitamin D and BMD in patients on enzyme inducing or non-enzyme inducing AED therapy

Variable	Enzyme-inducing (n = 27)	Nonenzyme-inducing (n = 23)	P–value
Duration of therapy (months)	32.78±33.86	31.43±32.08	0.307^{NS}
Vitamin D (ng/ml)	17.96±5.34	16.97±4.02	0.174^{NS}
BMD (hip)	0.835±0.066	0.852±0.086	0.376^{NS}
BMD (spine)	0.938±0.105	0.96±0.062	0.895^{NS}

Values are expressed as mean±SD, NS–not significant

Table 5: Serum 25-OH Vitamin D and BMD in patients on single or multiple AED therapy

Variable	Single therapy (n=10)	Multiple therapy (n=40)	P–value
Duration of therapy (months)	25.90±30.009	33.73±33.55	0.841^{NS}
Vitamin D (ng/ml)	17.53±3.63	17.50±5.04	0.303^{NS}
BMD (hip)	0.845±0.048	0.843±0.081	0.738^{NS}
BMD (spine)	0.952±0.030	0.947±0.098	0.413^{NS}

Values are expressed as mean±SD, NS–not significant

Table 6: Enzyme inducing/Non–enzyme-inducing AED therapy vs. Haematological parameters

Variable	Enzyme-inducing therapy (n = 27)	Non–enzyme-inducing therapy (n = 23)	P-value
RBC (cells/µl)	4.61±0.666 x 10^6	4.58±0.736 x 10^6	0.464^{NS}
Hb (g/dl)	12.78±2.15	12.15±2.12	0.793^{NS}
PCV (%)	39.22±4.44	38.03±4.73	0.665^{NS}

Values are expressed as mean±SD, NS–not significant

Single vs. multiple AED therapy

The mean RBC count, Hb and PCV in single AED therapy was higher when compared with multiple AED therapy, but it was not statistically significant represented in table 7.

Impact of duration of AED therapy on BMD and haematological parameters

Duration of anti-epileptic drug therapy was compared with BMD (spine and hip) of patients using multiple regression models

showed a negative correlation but was not statistically significant (P>0.05). The relationship between duration of AED therapy and haematological parameters (RBC, Hb, PCV) were analyzed using multiple regression models and it showed a negative correlation (r =-0.128), but it was not statistically significant.

AED therapy and its impact on morphology of RBC

In the study population, 40% showed microcytic hypochromic morphology, 4% showed macrocytic hypochromic morphology, 56% had normocytic normochromic morphology as identified by peripheral smear examination.

Table 7: Single/Multiple AED therapy vs. haematological parameters

Variable	Single therapy (n = 10)	Multiple therapy (n = 40)	P–value
RBC (cells/µl)	4.81±0.655 x 10^6	4.54±0.698 x 10^6	0.901^{NS}
Hb (g/dl)	13.03±2.34	12.36±2.09	0.833^{NS}
PCV (%)	40.34±5.98	38.26±4.13	0.341^{NS}

Values are expressed as mean±SD, NS–not significant

DISCUSSION

Epilepsy is a serious disorder of public health importance. Patients with epilepsy have a nearly two-fold increased risk of fractures vs. the general population. Long-term AED use causes multiple abnormalities in calcium and bone metabolism that have been most extensively described in institutionalized patients. Previous study reports indicate that 20-65% of epileptic patients receiving anticonvulsants developed signs of rickets or osteomalacia [1]. Osteoporosis and seizures are a common diagnosis in older adults and may occur concomitantly. In the older age group, the incidence of unprovoked seizures is 121 per 100,000 per year, and the diagnosis of epilepsy nears 40 per 100,000 per year. Hepatic enzyme induction by certain anticonvulsants medications seems to contribute to increased metabolism of 25-OH Vitamin D to inactive metabolites which results in metabolic bone disease according to other study findings [4].

Chronic therapy with AEDs is associated with Vitamin B_{12} and folic acid metabolisms. Further, they can also decrease the absorption of iron from the gut wall resulting in anaemia. The development of megaloblastic anaemia associated with anticonvulsant therapy is considered to be the result of folic acid deficiency. Another study postulated that anticonvulsant drugs produce folate deficiency by acting as weak folic acid antagonists [2].

Hence, this study was undertaken with a view to assessing the incidence of AED-related osteoporosis and anaemia and to provide patient education for those identified under risk for the same.

Totally 50 patients were enrolled in this study based on inclusion and exclusion criteria. Of these, 27 were males and 23 were females Based on WHO's definition for osteoporosis 16% patients had osteoporosis and 22% patients had osteopenia.

Similar to a previous study [1], a significant proportion (>50%) of patients had low serum 25-OH Vitamin D levels, but in contrast serum 25-OH Vitamin D levels showed a positive correlation with BMD values. Hence our study revealed the positive association of serum 25-OH Vitamin D with BMD values. It has been reported that certain drugs such as phenytoin and phenobarbital cause induction of hepatic microsomal enzymes resulting in increased catabolism of 25-OH vitamin D. The differences in serum vitamin D may be explained by differences in season, diet, sun exposure and latitude of the area in which the study was conducted.

Among the 50 study subjects, 20% were on single AED therapy, and 80% were on multiple AED therapy. The mean BMD (spine and hip) in single therapy group was higher compared with multiple therapy groups, but the difference was not statistically significant (P>0.05) probably due to our relatively short sample size and duration of the study.

In our study population, 54% were on enzyme-inducing drugs, and 46% were on non-enzyme inducing drugs. BMD of the enzyme-inducing class was less compared with non-enzyme inducing class (P>0.05) showing comparable decrements to a study [1] supporting the fact that enzyme-inducing AEDs have a negative impact on bone health.

The mean duration of AED therapy in our study was 32.16±32.17 mo (mean±SD). Duration of AED therapy was compared with BMD (spine and hip) of patients using multiple regression models showed a negative correlation, but we were not able to achieve statistical significance (P>0.05) findings suggest that the disease or associated therapy is instrumental in the deleterious skeletal profile.

Compared with the study [2] which showed an incidence of 15.38% of mild and 12.3% of moderate anaemia, our study showed 22% patients had mild and moderate anemia and 2% had severe anemia.

The relationship between duration of AED therapy and haematological parameters (RBC, Hb, PCV) showed negative correlation (r =-0.128) which was similar to the study [2] (showed negative correlation between duration of therapy and Hb value) but it was not statistically significant suggesting chronic therapy with AEDs have a negative association with haematological parameters. Further, we weren't able to assess the dietary habits, lifestyle, socio-economic status and adherence to the therapy of the study population.

The mean RBC count, Hb and PCV in single AED therapy were higher when compared with multiple AED therapy findings suggest that patients with multiple AED therapy have a greater risk for developing anaemia in later life. But we failed to achieve statistical significance which may be due to our short sample size and duration of the study.

The mean RBC count, Hb and PCV in enzyme-inducing AED therapy were higher when compared with non-enzyme inducing AED therapy. Such a conflicting result may be explained by confounding variables in our study such as adherence to therapy, dietary habits, duration of study and sample size, but our outcome showed no statistical significance.

Compared to the study [5] which demonstrated 11% incidence of macrocytosis, our study showed 40% microcytic hypochromic morphology, 4% macrocytic hypochromic morphology which may be due to deficiency of iron, folic acid, and vitamin B_{12} respectively with AED therapy. But further tests such as total iron binding capacity, serum ferritin, serum folic acid and vitamin B_{12} must be measured in order to confirm the deficiency.

Limitations of the study

1. Short sample size and duration of the study.

2. We couldn't assess the relationship between dietary habits, lifestyle and patient's sunlight exposure on serum vitamin D levels.

3. Study results could vary depending on the geographical region used for the study.

4. Reference values used may affect the results depending on the source

CONCLUSION

Epilepsy is a chronic non-communicable disorder of the brain that affects people of all ages. Approximately 50 million people worldwide have epilepsy making it one of the most neurological diseases globally. Chronic therapy with AEDs possesses a significant risk of developing osteoporosis and anaemia. The incidence rate varies depending on the type and/or mode of therapy. It is also dependent on the duration of therapy. Early detection and timely management through diet and lifestyle modifications or pharmacotherapy will reduce the incidence of unwanted effects due to AEDs and improve the quality of life of patients.

With our study, we were able to determine the occurrence of osteoporosis and anaemia in south Indian population who were on chronic AED therapy. In conclusion, those patients were identified and provided with the patient information brochure which may help them to improve their functional outcome and reduce the occurrence of osteoporosis and anaemia due to chronic AED therapy.

CONFLICT OF INTERESTS

Declared none

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