ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Effect of Antiepileptic Drug Therapy on Bone Metabolism and its Relationship with Vitamin D Receptor Gene

Antiepileptik İlaç Tedavisinin Kemik Metabolizması Üzerine Etkisi ve D Vitamini Reseptör Geni ile İlişkisi

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ABSTRACT Objective: The relationship between antiepileptic drugs and bone health and also the genetic aspect of this relationship is not clear and has been investigated in recent years. The aim of this study was to determine the effects of different antiepileptic drugs (AEDs) on bone mineral density results in long term follow up and to evaluate the relationship with the vitamin D profile (Bsml mutation) of the patients. **Material and Methods:** Eighty ambulatory patients (21 male, 59 female; mean age: 9.1±3.85 years) were included in the study. The patients were divided into four groups; Group 1 (levetiracetam), Group 2 (Carbamazepine), Group 3 (Valproic acid) and Group 4 (control). The plasma calcium, phosphorus, parathyroid hormone, alkaline phosphatase, vitamin D levels and bone mineral density values of femur and spine (L1-4) were compared. The patients were divided into two groups according to vitamin D receptor genes as the patients with Bsml mutations and without (wild type) Bsml mutations. **Results:** The difference between bone mineral density, Z score, phosphorus, parathyroid hormone, alkaline phosphatase and vitamin D levels of the patients in all four groups was not statistically significant. The phosphorus, parathyroid hormone, alkaline phosphatase and vitamin D levels and bone mineral density and Z score results of the patients with and without Bsml mutations were not significantly different. **Conclusion:** In this cross-sectional analysis, we found that the bone mineral status of the patients receiving different AEDs for a long time (> 2 years) was not significantly different. There was also no loss of bone mineral content in the patient group when compared with age-appropriate controls. According to the results of this study, Bsml polymorphism is not determinant in the progression of bone mineral loss.

Keywords: Antiepileptic drug; bone mineral density; epilepsy

ÖZET Amaç: Antiepileptik ilaçlar ile kemik sağlığı arasındaki ilişki, ayrıca bu ilişkinin genetik yönü net değildir ve son yıllarda araştırılmıştır. Bu çalışmanın amacı, farklı antiepileptik ilaçların uzun süreli takiplerde kemik mineral yoğunluğu sonuçları üzerine etkilerini belirlemek ve hastaların D vitamini profili (Bsml mutasyonu) ile ilişkilerini değerlendirmektir. **Gereç ve Yöntemler:** Çalışmaya 80 gezici hasta (21 erkek, 59 kız; yaş ort: 9,1±3,85 yıl) dahil edildi. Hastalar dört gruba ayrıldı; Grup 1 (Levetirasetam), Grup 2 (Karbamazepin), Grup 3 (Valproik asit) ve Grup 4 (kontrol). Plazma kalsiyum, fosfor, paratiroid hormonu, alkalen fosfataz, D vitamini düzeyleri ve femur ve vertebra (L1-4) kemik mineral yoğunluğu değerleri karşılaştırıldı. Hastalar D vitamin reseptörü genlerine göre Bsml mutasyonu olan ve (vahşi tip) Bsml mutasyonu olmayan olarak iki gruba ayrıldı. **Bulgular:** Dört grubun hepsinde kemik mineral yoğunluğu, Z skoru, fosfor, paratiroid hormonu, alkalen fosfataz ve D vitamini düzeyleri arasındaki fark istatistiksel olarak anlamlı değildi. Bsml mutasyonu olan ve olmayan hastaların fosfor, paratiroid hormonu, alkalen fosfataz, D vitamini düzeyleri ve kemik mineral yoğunluğu ve Z skorları arasında anlamlı fark yoktu. **Sonuç:** Bu kesitsel analizde, farklı antiepileptik ilaçları uzun süreli (>2 yıl) alan hastaların kemik mineral durumunun önemli ölçüde farklı olmadığını saptadık. Ayrıca yaşa uygun kontrol grubu ile kıyaslandığında hasta grubunda kemik mineral içeriği kaybı yoktu. Bu çalışmanın sonuçlarına göre Bsml polimorfizmi, kemik mineral kaybının ilerlemesinde belirleyici değildir.

Anahtar Kelimeler: Antiepileptik ilaç; kemik mineral yoğunluğu; epilepsi

Epilepsy is a common disorder affecting 5-10/100 person in general population.[1] Several large series have shown that patients with epilepsy has tendency to bone fractures compared to general popula-

tion.[2] In a recent study about the bone status of epileptic patients; antiepileptic drug (AED) usage has found to be the most important determinant in the fracture risk of ambulatory adult epilepsy patients.[3] The mechanism of this bone impairment has been explained as vitamin D dependent and independent manner in that study.[3] However studies in childhood are very limited. In a recent study conducted in ambulatory patients receiving AED treatment for 6 months in pediatric age, the authors divided AED taking patients to enzyme inducing and non inducing groups and concluded that valproic acid (VPA) may be safer.[4] That group also firstly has reported the bone parameters of the epileptic patients without anamnesis of AED usage and has concluded that bone mineral density (BMD) was not affected in these children.[4] There are very limited studies about long term results of different AED types in bone health and this is the first study indicating these relationships with association of Bsml polymorphism in the literature as far as we know. The aim of this study was to evaluate the effects of long term AED treatment on bone mineral density results of the patients and the relationship with Bsml polymorphism.

MATERIAL AND METHODS

PATIENTS

The study was approved by Local Ethics Committee (Number: 02/09/2013) and informed consent of the patients (parents') was obtained. Eighty ambulatory patients (21 male, 59 female; mean age: 9.1±3.85 years) and a control group (6 male, 16 female; mean age: 6.4±2.7 years) were included in the study. The seizure type of the patients was decided according to the International League Against Epilepsy (ILAE) criteria.[4] The patients were receiving necessarily the same antiepileptic drugs (AED) for at least two years and the patients with mental retardation or cerebral palsy (CP) (ambulatory patients) were not involved.

Exclusion criteria included being below two years age, having mental retardation or cerebral palsy, or any other diseases that might affect bone health (hypo or hyperthyroidism, renal, hepatic or gastrointestinal diseases, hypogonadism, malnutrition/malabsorbtion), using medications that may influence bone metabolism (steroid drugs, ect), supplements or calcium (Ca) intake, family history of genetic diseases affecting bone mineral metabolism.

GROUPS

The patients were divided in four groups according to the AEDs used as Group 1 (Carbamazepine n=18), Group 2 (Valproic acid, n=24), Group 3 (Levetiracetam, n=16) and Group 4 (control, n=22).

LABORATORY TESTS

Plasma Ca, phosphorus (P), PTH (parathyroid hormone), ALP (alkaline phosphatase), vitamin D levels of patient and control groups were measured from plasma samples. Plasma 25-OH D vitamin levels were calculated by means of HPLC (High performance liquid chromatography) method and HPLC (Shimadzu RF-10AxL) device. Intra-assay CV: 2.6% and Inter-assay CV: 3.6% respectively.

Reference Intervals

Summer 50-300 nmol/L (20-120 ug/L)

Winter 25-100 nmol/L (10-60 ug/L)

BONE MINERAL DENSITY ANALYSIS

The bone mineral density (BMD) analysis was performed from the femur and vertebra regions by a dual energy X-ray absorptiometry device (Discovery XR, Hologic). The total femur and L1-4 vertebra BMD levels were considered for comparison. Additionally the femur and vertebra Z score levels were compared. Z scores were retrieved from the comparison of the data base (age and gender matched control subjects) and patients' results in densitometry device. In this study we consider Z score levels because that is recommended analysis for children and Z score levels under -2 are considered as low and over -2 are considered normal.

VDR GENOTYPING

Peripheral blood samples (2cted in EDTA tubes from all participants and stored at -20 °C until processing. Genomic DNA was extracted from the frozen EDTA-blood samples by usingthe Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI) according to the manufacturer's recommendations. After extraction, the quality and quantity of DNA were estimated using NanoDrop Spectrophotometer (Maestrogen, MaestroNanodrop, USA). DNA samples were stored at -20°C until analysis. Genotyping for VDR Bsml polymorphism (ID:C_8716062_10, rs1544410) was performed using TaqManAllelic discrimination assay on an ABI 7500 Fast Real Time PCR System (Applied Biosystems, Foster City, CA). Reactions were carried out according to the manufacturer's protocol (TaqMan SNP Genotyping Assays). The PCR consisted of an initial step at 60°C for 30 s, hold stage at 95°C for 10 min, PCR stage for 40 cycles: at 95°C for 15 mins, at 60°C for 1 min, and a read stage after at 60°C for 30 s.Analysis for interpretation was performed using TaqManGenotyper® Software™, V2.01.

BSML STATISTICS

In order to compare the laboratory and BMD and score results Kruskal Wallis test and Mann Withney U tests were performed and $p<0.05$ was considered statistically significant.

RESULTS

The mean age, Ca, P, ALP, vitamin D, PTH levels and femur and vertebra score and BMD levels are summarized in Table 1 according to groups.

The mean femur and vertebra BMD levels of the groups Group 1 (0.77±0.2; 0.69±0.2 respectively), Group 2 (0.61±0.13; 0.57±0.17 respectively), Group 3 (0.65±0.18; 0.57±0.17 respectively) and Group 4 (0.59±0.16; 0.51±0.14) were not significantly different ($p>0.05$) except Group 2 which had patients with older age. Similarly other laboratory parameters (Ca, P, ALP, vitamin D and PTH levels were not different between four groups ($p>0.05$).

The mean femur and vertebra BMD and Z score levels of the patients with and without Bsml polymorphism were not significantly different ($p>0.05$) (Table 2, Figure 1).

DISCUSSION

In this study sufficient number of the patients in divided groups were involved for driving a conclusion and we concluded that the BMD changes related to the long term AED treatment are not present in the

TABLE 1: The demographics, laboratory, BMD and Z score results of the patients according to groups.

	CBZ (n=18)	VPA (n=24)	LEV (n=16)	CONT(n=22)	TOTAL (n=80)
Age	11.4±3.2	8.4±3.8	8.69±3.5	6.4±3.5	8.6±3.74 years
Gender	11/7	12/12	10/6	16/6	59F/21M
Ca	9.35±0.63	9.5±0.54	9.46±0.32	9.8±0.4	9.5±0.5
P	4.8±0.6	4.9±0.6	4.56±0.8	4.9±0.6	4.8±0.6
Vitamin D	23.7±22.7	22.7±18.5	25.5±16.6	23.1±6.8	23.6±16.6
ALP	248.2±128	203.44±82.12	234.5±114.4	181±32	213.7±94.7
PTH	50.6±24.4	41.65±25.09	49.23±28.6	37±15	43.9±23.5
Femur BMD	0.76±0.2	0.61±0.13	0.65±0.18	0.59±0.16	0.65±0.17 gr/cm^2
Vertebra BMD	0.68±0.2	0.57±0.17	0.57±0.17	0.51±0.14	0.59±0.18 gr/cm^2
Femur Z score	-0.66±1.1	-1.04±1.3	-1.07±1.05	-0.8±1.06	-0.9±1.4
Vertebra Z score	-0.42±1.3	-0.6±1.04	-0.85±0.98	-0.55±0.9	-0.6±1.04

LEV: Levetiracetam; CBZ: Carbamazepine; VPA: Valproic acid; CONT: Control; Ca: Calcium; P: Phosphorus; ALP: Alkalin phosphatase; PTH: Parathyroid hormon; BMD: Bone mineral density.

TABLE 2: The demographics, laboratory, BMD and Z score results of the patients according to Bsml polymorphism.

	bb (n=22)	Bb (n=26)	BB (n=10)	p
Age	8.9±3.4	9.6±3.4	10±4	
Gender	14/8	17/10	3/7	
Ca	9.35±0.63	9.5±0.6	9.4±0.39	
P	4.8±0.59	5±0.5	4.56±1.08	
Vitamin D	18.6±12.4	24.6±3.5	33.1±30	
ALP	215.3±111.7	251.48±92.97	187.4±125.5	
PTH	48.1±17.8	50.05±31.36	33.87±22.58	
Femur BMD	0.69±0.2	0.67±0.18	0.63±0.2	0,297
Vertebra BMD	0.60±0.19	0.61±0.17	0.63±0.23	0,087
Femur Z score	-0.55±1.1	-1.07±1.3	-1.4±1.38	0,488
Vertebra Z score	-0.6±0.9	-0.6±0.9	-0.9±0.48	0,724

bb: Homozigot wild type; Bb: Heterozigot Bsml; BB: Homozigot Bsml polymorphism; Ca: Calcium; P: Phosphorus; ALP: Alkalin phosphatase; PTH: Parathyroid hormon; BMD: Bone mineral density.

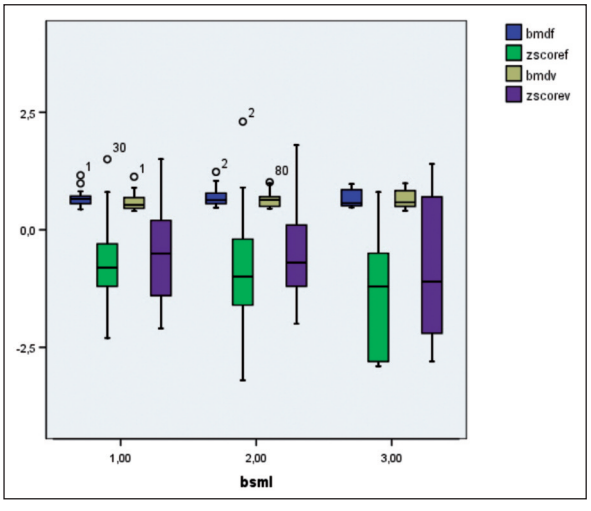

FIGURE 1: The BMD levels of the patients with and without Bsml polymorphism both in femoral and vertebral region.

childhood ages. The included AEDs' effects on bone parameters were not different at more than two years under treatment. Unfortunately this study could not include the changes in BMD results before and after treatment because this study was cross sectional. Additionally there is no relationship and difference for patients bearing Bsml mutations compared to wild type patients. Biochemical markers related to bone health were not different also compared to the controls and children taking AEDs for longer than 2 years in this study.

In contrast to our findings, previous reports have indicated that biochemical markers are affected in approximately 30-40% of the patients.[5] Additionally in a previous study these changes were observed as early as 60 days after the onset of treatment.[6] In a recent study, this biochemical impairment has been attributed to the low calcium intake of the epileptic patients on AED treatment.[5] However we did not observe such a change in pediatric patients. In fact it is not easy to standardize the calcium intake of the patients since they have different families and eating habits but at least we could exclude the children with anamnesis of taking vitamin and other supplements as in other studies. In that study also the vitamin D levels of the patients taking AED treatment have found to be low in nearly two thirds of the patients (%58.1) and they attributed this finding to low sunlight exposure that was also the case in the control group.[5] Sunlight exposure is also another factor that might affect both vitamin D levels and other biochemical parameters and BMD in the patients in such studies. Also sunlight exposure cannot be optimized and standardized in patients as in this study however we might claim that the subjects and patients in this study possibly do not have considerably insufficient sunlight exposure since our country has optimal climate (vitamin D levels in controls was 22±7 microgr/L). Physical activity, aging and female sex are

considered to be the other predictive factors for BMD loss in epilepsy in adult patients.[3] Physical activity profile in patients also may be heterogeneous and cannot be standard for all patients however the ambulatory patients were all subjects of this study and patients with CP may be the subjects of another study.

In enzyme inducing drugs the possible mechanism is relatively clear; hepatic enzyme induction resulting in increase in vitamin D metabolism.[7] Hamed et al. have shown that the adult patients on AED treatment are prone to bone loss, vitamin D deficiency and biochemical alterations results in increase in bone turnover.[3] They observed osteoporosis of femoral neck in 21% of their subjects and 72% in lumbar spine as a result.[3] However we did not observe alterations related to biochemical markers related to bone health as well as BMD although we did not investigate OPG or RANKL.

Valproic acid is a non-enzyme inducing agent thus do not cause increase in vitamin D catabolism and in a recent study in pediatric subjects this AED have presented to be a bone protecting one.[8] Levatiracetam is also a non-enzyme inducing AED and have been investigated to be safer regarding bone health previously and have concluded to be in a previous study.[9] However Serin et al. have shown that the effects of valproic acid or levatiracetam on bone health parameters are not different compared to enzyme inducing carbamazepine in long term (>2 years) intake in pediatric patients.[10] In contrast to this result Phabphal et al. have concluded that switching to levatiracetam might cause significant improvement of the BMD and increase in the vitamin D levels in their controlled study in young adults.[11] They have decreased the ratio of osteoporosis 32% versus 57% in the patients who switched to levatiracetam treatment however BMD continued to decrease in patients who continue to phenitoin.[11]

Treatment for prevention of osteoporosis in patients taking AEDs have been investigated and Lazzari et al. compared placebo and supplementation (Ca and vitamin D) group and have achieved favorable results in 65% of their patients and recommended supplementation.[12] They also have pointed out that this study population is also prone to tobacco and alcohol use and vertebral fractures and have suggested routine follow up of BMD.[12]

Previously Bsml mutation of vitamin D receptors has been investigated in men and premenopausal women and vitamin D-parathormone pathway associated lower bone mass has been reported.[13] Other studies have reported a relationship between low BMD in epileptic patients and B allele of Bsml polymorphism related to VDR gene.[14,15] However in this study with pediatric subjects on long term AED treatment we could not identify a relationship between BMD loss and Bsml polymorphism although study group was not large enough as a genetic analysis. Additionally bone loss was not present according to mean BMD and Z score values in our groups. This may be a consequence of investigating the results of pediatric age and osteoporosis may be a problem in mainly adult ages. However investigation of other genetic predispositions may be more beneficial in this group of patients as a consequence of our results. Previously COL1A1 SP1 gene polymorphism has been found to be related to osteoporosis in postmenopausal women.[16] Villegas-Martinez et al. have documented a strict relationship between low BMD and COL1A1 mutation which is not affected by gender and menstrual status.[17] Another polymorphism "CYP 2C9 2 and 3" have been identified to be affecting BMD.[18] This polymorphism has found to be associated with higher serum PTH levels, vitamin D levels and higher BMD independent of plasma phenytoin levels in a previous study in adult epileptic patients using phenytoin.[19]

The study has some limitations. First is the cross sectional design which limits observation of the decrease in BMD of the subjects. The best analytic way is to provide a baseline BMD for each subject and obtain follow up. Prospective series especially for pediatric subjects with longer duration

of therapy is needed about this subject. The common limitations of that kind of studies are valid also for this study; lack of standardization of Ca intake, sun exposure and physical activity. Additionally the number of patients may be considered insufficient for a genetic analysis.

CONCLUSION

The main outcome of this study is that Bsml polymorphism was not associated with BMD or the other bone parameters in our study population. The effects of different AEDs in long term follow up as a monotherapy were not different on biochemical bone parameters and BMD in children.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hepsen Mine Serin, Zehra Pınar Koç;* ***Design:*** *Özlem Özcanlı Çay, Hepsen Mine Serin;* ***Control/Supervision:*** *Hepsen Mine Serin, Zehra Pınar Koç, Erdal Yılmaz;* ***Data Collection and/or Processing:*** *Özlem Özcanlı Çay, Deniz Erol;* ***Analysis and/or Interpretation:*** *Hepsen Mine Serin, Zehra Pınar Koç;* ***Literature Review:*** *Özlem Özcanlı Çay, Deniz Erol;* ***Writing the Article:*** *Özlem Özcanlı Çay, Hepsen Mine Serin, Zehra Pınar Koç;* ***Critical Review:*** *Deniz Erol, Erdal Yılmaz, Zehra Pınar Koç;* ***References and Fundings:*** *Özlem Özcanlı Çay, Deniz Erol;* ***Materials:*** *Özlem Özcanlı Çay, Hepsen Mine Serin.*

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