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The bone mineral content alterations in pediatric patients medicated with levetiracetam, valproic acid, and carbamazepine

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ABSTRACT

Aim: The negative effect of antiepileptic drugs on bone health has been previously documented. However, which antiepileptic drug is safer in regard to bone health is still questionable. Our aims were to investigate the bone mineral density alterations in pediatric patients who receive antiepileptic medication for a minimum of two years and to compare the results of these drugs.

Materials and methods: Fifty-nine patients (32 males, 27 females; mean age: 8.6 ± 4.6 years) and a control group (13 males, 7 females; mean age: 7.6 ± 3.3 years) were included in the study. The patients were receiving necessarily the same antiepileptic drugs (AEDs) for at least two years, and none of the patients had mental retardation or cerebral palsy. The patients were divided into three groups: group 1 (patients receiving levetiracetam (LEV), n = 20), group 2 (patients receiving carbamazepine (CBZ), n = 11), and group 3 (patients receiving valproic acid (VPA), n = 28). Plasma calcium (Ca), phosphorus (P), parathyroid hormone (PTH), alkaline phosphatase (ALP), vitamin D levels, and bone mineral density (BMD) values of femur and vertebras (L1-4) and z-scores (comparative results of BMD values of the patients with the age- and gender-matched controls in device database) of the groups were compared.

Results: The differences between P, PTH, ALP and age, Ca and BMD results, and vitamin D levels of the patients in all four groups was not statistically significant according to Kruskal–Wallis test ($p > 0.05$). The z-score levels of all the patient and control groups were also not statistically significantly different compared with each other.

Conclusion: In contrast to previous reports in pediatric patients, our study has documented that there is not a considerable bone loss in patients receiving long-term AED medication. Although levetiracetam has been proposed as bone-protecting medication, we did not observe any difference between AEDs regarding bone mineral density after two years of treatment.

1. Introduction

Many antiepileptic drugs (AEDs) are associated with decrease in bone mineral density (BMD) as documented in numerous previous studies [1–3]. The BMD decrease associated with some AEDs is attributed to the increased enzyme induction and expression of cyp24 which lead to increased inactivation of vitamin D [4]. Recent studies have confirmed that the decrease in BMD levels is associated with a B allele of vitamin D receptor genotype [4]. It has been postulated that new-generation AEDs like levetiracetam (LEV) have no harmful effect on bone health [5]. However, animal studies have pointed out the negative effect of the drug on bone strength without decreasing the BMD, and another study has addressed the decrease in BMD associated with LEV [6, 7]. There have not been any studies in the literature comparing the effects of these drugs on BMD in long-term (>2 years) usage in pediatric population. In this study, We therefore investigated and compared the effects of LEV, CBZ, and VPA on bone health in pediatric patients.

2. Materials

2.1. Patients

This study was approved by Fırat University Ethical Committee, and informed consent of the patients' parents was obtained. Fifty-nine patients (32 males, 27 females; mean age: 8.6 ± 4.6 years) and a control group consisting of healthy subjects (13 males, 7 females; mean age: 7.6 ± 3.3 years) were included in the study. All of the patients were ambulatory without motor deficits who had received the same AEDs for at least two years. They received no additional medication, vitamin or supplements, and none of the patients had mental retardation or cerebral palsy. The patients included in the study, additionally, did not receive

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Table 1
The demographics, laboratory, and BMD and z-score results of the patients according to groups.

	LEV (n = 20)	CBZ (n = 11)	VPA (n = 28)	Cont (n = 20)	Total (n = 59)
Age (years)	8.15 ± 3.3	10.5 ± 2	8.11 ± 3.95	7.6 ± 3.3	8.6 ± 3.5
Gender (female/male)	6/14	4/7	17/11	7/13	27F/32M
Ca (8.5–10.8 mg/dL)	9.38 ± 0.35	9.6 ± 0.66	9.42 ± 0.44	9.5 ± 0.2	9.4 ± 0.46
P (2.6–4.5 mg/dL)	4.7 ± 0.6	4.8 ± 0.4	4.9 ± 0.5	4.8 ± 0.8	4.8 ± 0.5
Vitamin D (20–150 μg/L)	22.8 ± 11.08	20.19 ± 7.02	19.5 ± 8.1	21.9 ± 7	20.8 ± 9.01
ALP (30–120 U/L)	218.8 ± 110.15	274.27 ± 104.86	202.36 ± 65.87	183.7 ± 50.9	221.3 ± 92.7
PTH (19.8–74.9 pg/mL)	47.9 ± 21.7	49.47 ± 18.45	44.29 ± 20.04	35.1 ± 13	46.5 ± 20.1
Femur BMD (g/cm^2)	0.55 ± 0.16	0.64 ± 0.11	0.6 ± 0.13	0.58 ± 0.13	0.59 ± 0.14
Vertebra BMD (g/cm^2)	0.53 ± 0.17	0.62 ± 0.098	0.58 ± 0.13	0.53 ± 0.13	0.56 ± 0.15
Femur z-score	−1.55 ± 2.3	−0.96 ± 0.11	−1.09 ± 1.25	−1.13 ± 1.16	−1.23 ± 1.7
Vertebra z-score	−0.97 ± 1.2	−0.29 ± 1.1	−0.56 ± 1.07	−0.63 ± 0.9	−0.64 ± 1.13

LEV: levetiracetam, CBZ: carbamazepine, VPA: valproic acid, cont: control, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, PTH: parathyroid hormone, BMD: bone mineral density.

any other AEDs previously other than their current drug. The control group consisted of healthy subjects who were seen at the hospital for another reason, and neither had any illness affecting bone health nor had received any medication and vitamin and supplements. Exclusion criteria were being below two years of age or having mental retardation or any chronic disease or receiving any medication besides AEDs.

2.2. Groups

The patients were divided into three groups: group 1 (patients receiving levetiracetam (LEV), n = 20), group 2 (patients receiving carbamazepine (CBZ), n = 11), and group 3 (patients receiving valproic acid (VPA), n = 28).

3. Methods

3.1. Laboratory tests

The plasma calcium (Ca), phosphorus (P), parathyroid hormone (PTH), alkaline phosphatase (ALP) and vitamin D levels of the patient groups and control groups were measured from plasma samples.

3.2. Bone mineral density analysis

The bone mineral density (BMD) analysis was performed from the femur and vertebra regions by using a dual energy X-ray absorptiometry device (Discovery Xi, Hologic). The total femur and L1-4 vertebra BMD levels were considered for comparison. Additionally, the femur and vertebra z-score levels (obtained by comparison of the patients' BMD results and age-matched healthy subjects' results in the device database) were compared. Z-score levels below −2 were accepted as low bone mass. This was a cross-sectional study, and the basal BMD analysis was not performed on the patients.

3.3. Statistics

In order to compare the laboratory and BMD and score results, the Kruskal–Wallis test and the Mann–Whitney U-test were performed, and $p < 0.05$ was considered statistically significant. In each pairwise comparison, there was no significant difference between z-score and BMD levels. Although the number of patients in the groups was not homogenous according to Levene's test for equality of variances, the groups' results were homogenous ($p < 0.05$).

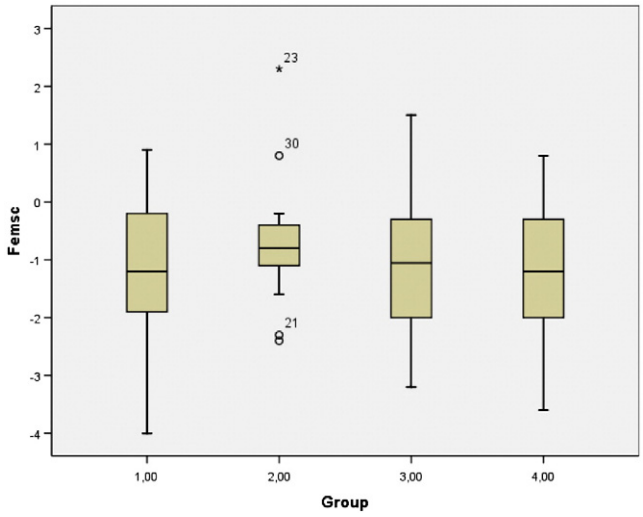
4. Results

The differences between Ca, P, PTH, ALP, and vitamin D levels of the patients in all four groups was not statistically significant ($p < 0.05$). The mean ± SD values of age, Ca, P, PTH, ALP, vitamin D levels, and BMD and scores are summarized in Table 1. The age, BMD levels, and z-scores of the patient and control groups were also not significantly different for both femur and vertebra regions (0.05) (Graphs 1 and 2).

5. Discussion

According to our results among the AEDs, None of the patients receiving AEDs had a significant change in z-scores. Although in the LEV treatment group there was a slight decrease in the scores, the difference was not considered significant. This is an important observation since there has been a growing trend towards the usage of LEV in patients, especially in those who tend to have a decrease in BMD levels. In a previous study, the patients on other AEDs were switched to LEV in order to increase their BMD; in that study, it was achieved in one year follow-up [8]. However, the patient group consisted of young adults (20–40 years of age), which does not reflect the pediatric patient group. The previous animal studies have predicted that the detrimental effects of AEDs on BMD might be observed in pediatric patients [7]. There was no significant effect of 2-year intake of AEDs on bone health as measured by BMD and score levels in our cohort of pediatric patients. However, the reason may be that the effects of the drugs manifest in later years or with longer exposure; thus, the effect of AED medication in adulthood BMD has to be analyzed in large study groups in prospective studies.

A previous review on bone health and AEDs recommended evaluating changes in bone metabolism in patients with epilepsy [9]. In particular, basal vitamin D levels and BMD levels and scores should be evaluated and supplemented if necessary in this population. Although increased



Graph 1. The z-scores of the patient and control groups in the femoral region.