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FULL-LENGTH ORIGINAL RESEARCH

Bone mineral density in a population of children and adolescents with cerebral palsy and mental retardation with or without epilepsy

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Summary

Purpose: The present study aimed to assess bone mineral density (BMD) in a population of children and adolescents with cerebral palsy and mental retardation with or without epilepsy.

Methods: One hundred thirteen patients (63 male and 50 female) were recruited for evaluation. Patients were divided in three groups: 40 patients (group 1) were affected by cerebral palsy and mental retardation; 47 (group 2) by cerebral palsy, mental retardation, and epilepsy; and 26 (group 3) by epilepsy. The control group consisted of 63 healthy children and adolescents. Patients underwent a dual-energy x-ray absorptiometry (DEXA) scan of the lumbar spine (L1–L4), and z-score was calculated for each patient; t-score was considered for patients 18 years of age and older.

Key Findings: Abnormal BMD by DEXA was found in 17 patients (42.5%) in group 1, in 33 (70.2%) in group 2, and in 3 (11.5%) in group 3. In groups 1 and 2, tetraparesis and severe/profound mental retardation were related to a significantly abnormal BMD ($p = 0.003$). The multivariate analysis of independent factors on BMD (z-score) revealed a significant correlation between BMD (z-score) and age ($p = 0.04$), body mass index (BMI; $p = 0.002$), severe/profound mental retardation ($p = 0.03$), and epilepsy ($p = 0.05$).

Significance: A significantly lower BMD z-score value was found in patients with cerebral palsy, mental retardation, and epilepsy compared with those without epilepsy. The epileptic disorder appears to be an aggravating factor on bone health when comorbid with cerebral palsy and mental retardation.

KEY WORDS: Osteopenia, Osteoporosis, Anticonvulsant drugs, Dual x-ray absorptiometry.

Epilepsy is a neurologic disorder associated with many established comorbidities, one of which is a reduced bone health (Baroncelli et al., 2005). In fact, it is well known that changes in the normal functioning of the bone tissue, mostly insidious and asymptomatic, occur more frequently in patients with epilepsy than the general population (Hunter et al., 1971; Medlinsky, 1974; Weisman et al., 1979; Petty et al., 2007; Samaniego & Sheth, 2007).

In patients with epilepsy there is indeed a convincing evidence of biochemical abnormalities indicating a disturbed bone metabolism, a decreased bone density, and a 2–6 times increased risk of fractures compared to the general population (Henderson et al., 2002; Beerhorst et al., 2005). These bone disorders may be linked to multiple factors, the most relevant of which appear to be coexisting cerebral palsy, mental retardation, reduced physical activity, inappropriate dietary habits with insufficient vitamin D intake, reduced exposure to sunlight, and prolonged treatment with antiepileptic drugs (Guo et al., 2001; Sato et al., 2001; Farhat et al., 2002; Sheth, 2004).

On the other hand, some of these factors, such as cerebral palsy (Morijiri & Sato, 1981; Lee et al., 1989; Shaw et al., 1994; King et al., 2003; Houlihan & Stevenson, 2009; Mergler et al., 2009) and/or mental retardation (Haas et al., 1997; Center et al., 1998; Angelopoulou et al., 2000; Mugica et al., 2002; Budden & Gunness, 2003; Schrager, 2006; Coppola et al., 2007; González-Agüero et al., 2011; Roende et al., 2011; Srikanth et al., 2011), can be responsible for an altered state of bone mineralization.

In a previous study, Coppola et al. (2009) assessed bone mineral density (BMD) in a large population of children, adolescents, and young adults with epilepsy alone or in association with cerebral palsy and/or mental retardation.

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These authors found an abnormal BMD in approximately 60% of the patients, of whom 60% had osteopenia, and the remaining 40% had osteoporosis.

To shed light on the individual role played by epilepsy as a comorbid factor affecting bone status, a study was designed to compare bone mineral density in four groups of patients with the following: (1) cerebral palsy and mental retardation; (2) cerebral palsy, mental retardation, and epilepsy; (3) epilepsy; (4) a control group of healthy children and adolescents.

Methods

Patients were enrolled in the study according to the following inclusion criteria: (1) age 3 years and older; (2) diagnosis of cerebral palsy and mental retardation with or without epilepsy; (3) patients with epilepsy had to be taking monotherapy or polytherapy with antiepileptic drugs for at least 2 years; and (4) informed consent to participation in the study by parents/caregivers and/or, when possible, by patients.

The exclusion criteria were the following: (1) diseases involving primarily bone metabolism or familial history of bone metabolism disorders; (2) chronic treatment with drugs other than anticonvulsants; and (3) poor compliance with bone density evaluation.

The study received prior approval by the ethics committee of the medical faculty of the Second University of Naples, Italy, and informed consent was obtained directly from patient when possible and/or his/her parents/caregivers.

The subjects in the study group were enrolled from among patients followed in our clinic between January 2008 and March 2011. The control group consisted of 63 healthy children, adolescents, and young adults (23 male, 40 female), aged between 3 and 25 years (mean age 12.1 years). All patients and subjects in the control group were from the same region and had similar socioeconomic and calcium intakes.

Upon entry, each patient was evaluated for age, sex, weight, height, body mass index (BMI), and pubertal stage according to Tanner's classification. On the same day, a blood sample was obtained to evaluate serum calcium, phosphorus, alkaline phosphatase, total proteins, transaminases, gamma-glutamyltransferase (GGT), urea, creatinine, glucose, total red and white blood cells, platelet count, iron, transferrin, parathormone, thyroid-stimulating hormone (TSH), free triiodothyronine (ft3), free thyroxine (ft4), osteocalcin, calcitonin, vitamin D, and serum levels of antiepileptic drugs (AEDs). Furthermore, each patient's 24-h urine excretion of calcium and phosphorus was evaluated. All parents/caregivers were asked to fill out a questionnaire, designed to assess the patient's diet characteristics (i.e., calcium, carbohydrate, lipid and protein intake, and total amount of daily calories) and previous bone fractures. Each patient underwent a neurologic examination, and wake and sleep electroencephalography (EEG) recordings; the frequency and type of seizures, age at seizure onset, age at onset of AED therapy, duration of therapy, and type and number of AEDs were also evaluated.

Bone density was determined by dual-energy x-ray absorptiometry (DEXA) in the lumbar spine (L1–L4) using a Hologic QDR 1000 densitometer (Hologic Inc., Waltham, MA, U.S.A.). Individual BMD values were expressed as g/cm^2 and the t- and z-scores.

The children's lumbar spines (L1–L4) were examined while they were lying supine with the lower limbs partially raised to reduce lumbar lordosis. All patients were examined using the same scanner DEXA and in the same laboratory. When necessary, oral niaprazine (30 mg/dose) or intramuscular prometazine (25–50 mg/dose) were given approximately 30 min before the examination started to reduce motor hyperactivity.

According to the World Health Organization criteria, patients with scores that are 1–2.5 standard deviation (SD) below normal DEXA values have osteopenia, whereas those with values >2.5 SD below normal values are described as osteoporotic. The z-score, which was calculated by comparing the patient's SD with that of persons of the same age, was considered in all patients except for young adults, in whom the t-score, which was calculated by comparing the patient's BMD with young adult normative data, was considered. Normative data for sex, age, weight, and pubertal stage were generated by the same densitometer.

Descriptive statistics were performed by means and standard deviation; comparison of groups for continuous variables was performed by one-way analysis of variance, and Bonferroni test was used for multiple comparisons. The categorical variables were compared by means of Fisher exact test; a p-value of <0.05 was considered statistically significant.

All the statistical analyses were performed using StatXact-7-Cytel Studio Version 7.0.0 (Cytel Software Corporation Cytel Inc., Cambridge, MA, U.S.A.).

Results

One hundred thirteen patients were recruited in the study. Patients were divided in three groups: 40 patients (group 1) (25 male and 15 female, mean age 9.13 years) were affected by cerebral palsy and mental retardation; 47 patients (group 2) (22 female and 25 male, mean age 9.89 years) by cerebral palsy, mental retardation, and epilepsy; and 26 patients (group 3) (13 female and 13 male, mean age 12.88 years) by epilepsy only. The control group consisted of 63 healthy children, adolescents, and young adults (23 male, 40 female), aged between 3 and 25 years (mean age 12.1 years).

In group 1, cerebral palsy was represented by tetraparesis (17), spastic diplegia (14), and congenital hemiplegia (9). The mean BMI was 17.1 (range 9.1–31.4). A prepuberty condition was present in 32 patients (80%). Mental retardation was mild to moderate in 29, and severe/profound in 11

patients. Autonomous gait, including those walking with help, was present in 23 (57.5%).

In group 2, cerebral palsy consisted of tetraparesis (23), congenital hemiplegia (10), spastic diplegia (6), and dyskinetic palsy (8). The mean BMI was 17.3 (range 9.97–28.26). A prepuberty state was present in 32 patients (68.1%). Mental retardation was mild in six, moderate in six, and severe/profound in 35 patients. The epilepsy type was idiopathic generalized in 9, cryptogenic/symptomatic generalized in 14, idiopathic focal in 8, and cryptogenic/symptomatic focal in 16 patients. Four patients with perinatal hypoxic–ischemic brain injury and cerebral palsy were also affected by genetic syndromes (two Rett syndrome; one fragile X syndrome; one subtelomeric deletion of chromosome 1).

Mean age at seizure onset was 3.7 years (range 0.1–14 years), and mean age at therapy onset was 4.1 years (range 0.1–14.3 years). When evaluating BMD, 19 patients (40.4%) were seizure-free. Autonomous gait, including those walking with help, was observed in 19 patients (40.4%). The mean duration of epilepsy was 8.5 years (range 2.4–21 years), whereas the mean time taking anticonvulsant therapy was 3.0 years (range 0.3–20 years). Overall, seven patients (14.9%) had been taking a monotherapy (valproic acid [VPA], three; carbamazepine [CBZ], two; levetiracetam [LEV], one; phenobarbital [PB], one), and 40 (85.1%) a combination therapy (13, two drugs; 19, three drugs; 6, four drugs; 2, five drugs). The anticonvulsant drugs most frequently taken in combination were in decreasing order: VPA (39), CBZ (25), PB (15), and topiramate [TPM] (11). In group 3, the mean BMI was 21.57 (range 13.61–31.05). A prepubertal state was present in 15 patients (57.7%). Intelligence quotient (IQ) and neurologic examination were normal in all cases. The epilepsy type was idiopathic generalized in 9, cryptogenic/symptomatic generalized in 2, idiopathic focal in 4, and cryptogenic/symptomatic focal in 11.

Mean age at seizure onset was 6.7 years (range 2.3–13.3 years), and mean age at therapy onset was 7.28 years (0.5–14.5 years). The mean time on anticonvulsant regimen was 5.7 years (range 2.14–14 years). At the time of BMD evaluation, 21 patients (80.8%) were seizure- free. Overall, 18 patients (69.2%) were on monotherapy (VPA, 8; CBZ, 6; oxcarbazepine [OXC], 1; PB, 2; lamotrigine [LTG], 1), and 8 (30.8%) on polytherapy (4, two AEDs: VPA + LTG, VPA + TPM, CBZ + clobazam [CLB], VPA + CBZ, and 2, three AEDs: VPA + CBZ + vigabatrin [GVG], TPM + VPA + LTG).

Table 1 shows the statistical comparison of BMI, BMD, and z-score between the three groups by means of Bonferroni analysis of variance. A significant difference in BMI and in BMD emerged between groups 1 and 3, and 2 and 3, respectively ($p \leq 0.0001$ at Bonferroni test), whereas the z-score was found significantly different between the three groups (1 vs. 2, $p = 0.001$, 95% confidence interval [CI] 0.353–1.844; 1 vs. 3, $p = 0.024$, 95% CI −1.497 and −0.079; 2 vs. 3, $p = 0.0001$, 95% CI −2.489 and −1.285).

An abnormal BMD was found in group 1 in 17 patients (42.5%), with values showing osteopenia in 10 (25%) and osteoporosis in 7 (17.5%) (Table 2).

In group 2, an abnormal BMD was found in 33 patients (70.2%), including 24 with osteopenia (72.7%) and 9 with osteoporosis (27.3%).

In group 3, an abnormal BMD was found in three patients (11.5%), including two with osteopenia and one with osteoporosis.

In group 1 (cerebral palsy and mental retardation) and 2 (cerebral palsy, mental retardation, and epilepsy), tetraparesis and severe/profound mental retardation were both related to a significantly altered BMD ($p = 0.003$).

The multivariate analysis (Table 3) of independent factors on BMD (z-score) revealed a significant correlation between BMD (z-score) and age ($p = 0.04$), body mass index (BMI) ($p = 0.002$), and severe/profound mental retardation ($p = 0.03$). In more detail, mean z-score value was estimated to decrease by 0.07 with increasing age of 1 year, whereas z-score was estimated to increase by 0.06 each single point increase of BMI.

BMD (z-score) was significantly lower in group 3 with mental retardation, cerebral palsy, and epilepsy compared

Table 1. Statistical comparison of body mass index, body mineral density and z-score between the four groups by means of Bonferroni analysis of variance

	CP and MR patients	MR and CP and epilepsy	Epilepsy only	Control group
No. of patients	40	47	26	63
Sex	15 f, 25 m	22 f, 25 m	13 f, 13 m	40 f, 23 m
Mean age (years)	9.13 (4–18)	9.89 (3–21)	12.88 (8–25)	12.08 (3–25)
BMI (mean value, range)[a]	17.1 (9.1–31.4)[a]	17.3 (9.97–28.26)	21.57 (13.61–31.05)[a]	22.12 (14.1–42.22)
Prepuberty (%)	32 (80)	32 (68.1)	15 (57.7)	33 (52.4)
Puberty (%)	8 (20)	15 (31.9)	11 (42.3)	30 (47.6)
BMD (mean value, range)[b]	0.56 (0.327–0.997)	0.59 (0.371–1.04)[b]	0.76 (0.536–1.018)[b]	0.77 (0.449–1.387)
z-score (mean value, range)[c]	−0.83 (−3.4/+2.9)[c]	−1.69 (5.87/+1.06)[c]	−0.47 (−4.08/2.68)[c]	0.16 (−0.96/+2.64)

BMI, body mass index; CP, cerebral palsy; MR, mental retardation.
[a]BMI, groups 1 and 3 ($p \leq 0.0001$).
[b]BMD, groups 2 and 3 ($p \leq 0.0001$).
[c]z-score between the three groups (1 vs. 2, $p = 0.001$, 95% CI 0.353–1.844; 1 vs. 3, $p = 0.024$, 95% CI −1.497 and −0.079; 2 vs. 3, $p = 0.0001$, 95% CI −2.489 and −1.285).

Table 2. Comparison of clinical characteristics in groups 1, 2, and 3 based on BMD values

	Group 1		Group 2		Group 3	
	Normal-BMD	Abnormal-BMD	Normal-BMD	Abnormal-BMD	Normal-BMD	Abnormal-BMD
No. of patients (%)	23 (57.5)	17 (42.5)	14 (29.8)	33 (70.2)	23 (88.5)	3 (11.5)
Sex	10 f, 13 m	5 f, 12 m	9 f, 5 m	13 f, 20 m	12 f, 11 m	1 f, 2 m
BMI (mean value, range)	18.2 (10.5–31.4)	15.5 (7.45–25.1)	18.8 (11.8–25.09)	16.7 (11.03–28.3)	21.8 (13.61–31.05)	19.8 (18.44–21.38)
Mean age (years)	8.7 (4–15)	9.7 (4–18)	10.3 (3–21)	9.7 (3–19)	12.6 (8–25)	15.3 (13–18)
Cerebral palsy	23	17	14	33		
Tetraparesis (%)	4 (17.4)**	13 (76.5)**	4 (28.6)°°	19 (57.6)°°	–	–
Mental retardation	23	17	14	33		
Severe/profound (%)	2 (8.7)*	9 (52.9)*	7 (50)°	28 (84.8)°	–	–
Prepuberty (%)	19 (82.6)	13 (76.5)	9 (64.3)	23 (69.7)	15 (65.2)	0
Puberty (%)	4 (17.4)	4 (23.5)	5 (35.7)	10 (30.3)	8 (34.8)	3 (100)

BMI, body mass index; BMD, bone mineral density; group 1: cerebral palsy and mental retardation; group 2; cerebral palsy, mental retardation, and epilepsy; group 3: epilepsy only.
**p = 0.003; *p = 0.0003; °°p = 0.003; °p = 0.003 (at Fisher's exact test).

Table 3. Multivariate analysis of independent factors on BMD (z-score)

Model term	Estimate	SE	t-Statistic	p-Value
Intercept	−0.47	0.44	−1.06	0.288
Sex (as factor 1)	0.25	0.18	1.45	0.149
Age[a]	−0.07	0.04	−1.99	0.048
Puberty (as factor 1)	−0.07	0.31	−0.23	0.816
BMI[a]	0.06	0.02	3.22	0.002
Walking (as factor 1)	−0.41	0.61	−0.67	0.505
MR (as factor 1)	−0.35	0.59	−0.60	0.551
MR (as factor 2)[a]	−1.43	0.69	−2.08	0.039
CP (as factor 1)	0.07	0.56	0.12	0.903
Epilepsy (as factor 1)	−0.39	0.20	−1.95	0.052

MR, mental retardation; CP, cerebral palsy; BMI, body mass index.
Multiple R^2: 0.4373; Adjusted R^2: 0.4068.
[a]Statistical significance.

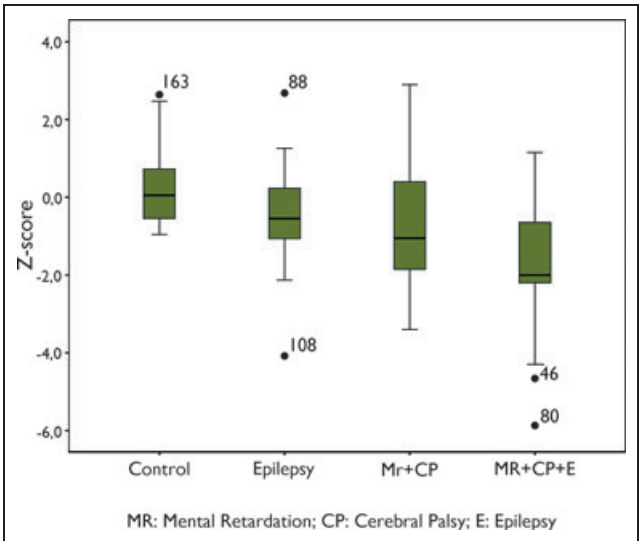

Figure 1.
Comparison of bone mineral density (BMD z-score) in groups 1, 2, and 3, and the control group. The horizontal lines represent medians for BMD z-scores.
Epilepsia © ILAE

to the other groups (Fig. 1). A history of bone fractures was absent in all patients.

Discussion

The present study has confirmed that epilepsy comorbid with cerebral palsy and mental retardation may worsen bone health in children and adolescents. Furthermore, a severe/profound mental retardation and spastic quadriplegia are significantly correlated to an abnormal bone mineral density (BMD) in patients with and without epilepsy.

A reduction in BMD was first reported in nine nonambulant patients with only cerebral palsy by Shaw et al. (1994), even when allowance was made for their body weight. In three of these patients with recurrent bone fractures, treatment with bisphosphonates lasting from 12 up to 18 months led to an increase in bone density of 20–40% with no apparent adverse side effects.

One year later, the BMD of 139 children with spastic cerebral palsy was reported by Henderson et al. (1995). BMD averaged nearly one standard deviation below the age-matched normal means for both the proximal parts of the femur and lumbar spine. Ambulatory and nutritional status best correlated with BMD. In another series, King et al. (2003) confirmed the prevalence of reduced BMD in children and adults with spastic quadriplegia. More recently, a systematic literature review (Mergler et al., 2009) reported a 4% per year incidence of fractures in children with moderate or severe cerebral palsy, whereas the prevalence of low BMD in the femur was 77%. Limited ambulation, feeding difficulties, previous fractures, anticonvulsant use, and lower body fat mass were associated with low BMD z-scores.

With reference to mental retardation as alone, Center et al. (1998) found a prevalence and risk factors for osteoporosis in 6% of female and 20% of male individuals in a community population of 94 young adults with mental retardation and mostly in subjects with Down syndrome. Seventeen percent of patients in this series were taking antiepileptic therapy. Overall, a number of risk factors were associated with a lower BMD, including small body size, hypogonadism, low vitamin D levels, and physical activity. Bone fractures occurred in 37% of females and 32% of males. These data were confirmed in other series of patients with Down syndrome (Angelopoulou et al., 2000; Mugica et al., 2002; González-Agüero et al., 2011).

Overlapping data were reported in patients with Angelman syndrome (Coppola et al., 2007), Rett syndrome (Roende et al., 2011), and Prader-Willi syndrome (Colmenares et al., 2011).

Regarding epilepsy, the impact of restriction of physical activity imposed by seizures (Guo et al., 2001) and the role of anticonvulsant drugs on bone metabolism (Sato et al., 2001; Farhat et al., 2002; Tsukahara et al., 2002) are well known. The effects of PB, phenytoin, CBZ, and VPA on bone mineralization have been repeatedly reported (Chung & Ahn, 1994; Kafali et al., 1999; Erbayat Altay et al., 2000; Verrotti et al., 2002; Ecevit et al., 2004; Sheth, 2004).

As to the so-called ''new AEDs,'' little is known about their effect on bone metabolism. So far, there are only two reports on the effect of LTG on BMD, alone or with VPA (Guo et al., 2001; Sheth & Hermann, 2007). These authors found that the treatment with VPA or LTG for >2 years was associated with short stature, low bone mass, and reduced bone formation. Recently, BMD was reported to be reduced in children treated with topiramate or CBZ when compared to the control group (Zhang et al., 2010).

To our knowledge, this is the first study in which the role of epilepsy was evaluated, by comparing two populations of patients with cerebral palsy and mental retardation, with and without epilepsy.

Remarkably, most of the patients in group 2, affected by epileptic encephalopathies and severe mental insufficiency, were treated with polytherapy, including mainly first-generation anticonvulsant drugs for several years.

Despite this, in our study, epilepsy showed a borderline significance at multivariate analysis ($p = 0.052$), probably due to the substantial weight exerted by other factors such as mental retardation and cerebral palsy, as well as the limited sample of our patients.

If the present comparative study confirms epilepsy to worsen bone health in patients with cerebral palsy and mental retardation, uncertainty still persists on the interpretation of these data.

First, the definition of osteopenia and osteoporosis in children and adolescents is still controversial. According to the World Health Organization, patients with scores that are 1–2.5 SDs below normal DEXA values have osteopenia, whereas those with values >2.5 SD below normal values are described as osteoporotic. Fracture risk doubles with every SD decrease in BMD (McCloskey et al., 2009).

However, these criteria suitable in adult age are less applicable in children and adolescents, because the threshold of fracture and the criteria for the diagnosis of osteoporosis/osteopenia based on BMD values, have not yet been established. In children and adolescents, the International Society for Clinical Densitometry (Lewiecki et al., 2008) suggested using the term ''reduced BMD values for chronological age'' when the densitometric values are ≤−2.0 SD compared to the reference values for age and sex, instead of osteopenia and osteoporosis, which should not appear in the reporting of a pediatric DEXA.

In this sense, the term ''bone mineral density at the lower limits of the normal range'' could be used for values of z-score between −1.0 and −2.0. The diagnosis of osteoporosis in children should not be based solely on the interpretation of densitometric measures, but it requires the simultaneous presence of a significant history of fractures and reduced bone mass values.

Finally, the correlation between the decrease/worsening of the z-score with increasing age can be explained at least in part by an increased exposure over time to negative factors such as epilepsy and the effects associated with cerebral palsy/mental retardation.

On the contrary, the favorable correlation between BMI gain and BMD z-score, was recently confirmed by Tandon et al. (2012), who reported that a greater skeletal growth and BMI gain in utero and during infancy are associated with higher peak body mass content, and a greater BMI gain in childhood and adolescence is associated with higher peak bone density. Although a potential role of genetic cofactors predisposing to bone demineralization cannot be ruled out, a familial history positive for abnormal bone health did not emerge in our series. Accordingly, a mild nephrolithiasis was disclosed in two patients only.

In conclusion, children and adolescents with cerebral palsy and mental retardation with and without epilepsy may have BMD values significantly lower than healthy controls.

Secondly, the epileptic disorder appears to be an aggravating factor on bone health when comorbid with cerebral palsy and mental retardation, although a somewhat facilitating role of more frequent severe/profound mental retardation in group 2 cannot be ruled out. Enzyme-inducing drugs, like phenytoin, PB, and CBZ, and also noninducing AEDs like VPA appear to have the strongest bone-depleting properties. Accordingly, the epilepsy group in our series was mostly treated with first-generation AEDs.

Another important issue is the correct interpretation of these data, especially in children, reserving the diagnosis of osteoporosis in carefully selected cases.

At present, being aware of the problem seems to be the most important issue, as well as assessing patient's BMD on an individual basis, providing antiosteoporotic treatment

(e.g., appropriate doses of 25 hydroxyvitamin D and calcium intake) to those who have developed a clear-cut bone loss, and last, but not least, promoting osteoprotective behavior among those who have not.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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