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Longitudinal Evaluation of Bone Mineral Density in Children Receiving Anticonvulsants

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Abnormalities in bone metabolism occurring in patients receiving chronic antiepileptic treatment have been reported in many studies. However, longitudinal bone mineral density (BMD) changes in children taking anticonvulsants have not been previously reported, to our knowledge. The subjects were 48 outpatients (aged 6 to 16 years) who were given a diagnosis of epilepsy. All subjects were treated with one or a combination of anticonvulsants (VPA, CBZ, or PB). We investigated longitudinal changes in the BMD using the Digital Imaging Processing (DIP) method and compared the BMD results with the duration of therapy and the chronological and bone age at the start of therapy. In all subjects, the standard deviation score of the BMD per year (ΔBMD-SDS/year) decreased remarkably after 11 years of age, compared with before 11 years of age. A significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy was observed in only one group treated with multiple drugs and assessed according to chronological age. No positive correlations were seen in any of the groups assessed according to bone age. Anticonvulsants therapy may reduce the rate of BMD increase, especially in adolescents who have been treated for long periods. Precise follow-up evaluations of the BMD are needed not only according to chronological age, but also according to bone age, which indicates the biological growth process much more accurately—especially before and during adolescence.

Key Words: bone mineral density, digital image processing method, anticonvulsants, bone age, longitudinal evaluation

Introduction

Abnormalities in bone metabolism occurring during chronic antiepileptic treatment with anticonvulsants have been reported in many studies since the initial report by Schmid et al, which was published in 1967[1], and the correlation between the onset of osteoporosis, characterized by a decrease in bone mineral density (BMD), and treatment with anticonvulsants has been widely discussed[2)~10)].

The BMD increases rapidly in a biphasic manner in childhood, especially during adolescence. We reported that the BMD as measured using the Digital Image Processing Method (DIP method) increased in a rapid biphasic pattern in both boys and girls during and after adolescence, and the BMD was more significantly correlated with the bone age, represented as the bone maturation score as an index of physical growth, than with the chronological age in adolescents[11]. The bone age was determined using the standard Japanese bone maturation scores.

We previously reported the results of BMD measurements performed using the DIP method in 98 children receiving anticonvulsants and concluded that when assessed according to the chronological age, the BMD of children receiving a single anticonvulsant consisting of either valproate sodium (VPA), carbamazepine (CBZ), or phenobarbital (PB) did not differ significantly according to the medication period (less than 4 years vs more than 4 years). However, a significant difference was observed for children taking multiple drugs. When assessed accord-

Table Chronological age, duration of therapy, and age at start of therapy in 4 groups according to medication.

	Sodium valproate (VPA)	Carbamazepine (CBA)	Phenobarbital (PB)	Multiple drugs
Number	11	19	5	13
Chronological age (years) (mean)	8.6-15.4 (12.4 ± 2.4)	6.8-16.3 (11.5 ± 3.1)	7.3-15.1 (9.7 ± 3.0)	9.6-15.9 (13.0 ± 1.7)
Duration of therapy (years) (mean)	1.4-12.3 (5.9 ± 3.4)	1.8-8.4 (4.1 ± 1.9)	2.9-10.9 (6.8 ± 2.9)	4.5-10.6 (7.4 ± 1.9)
Age at start of therapy (years) (mean)	2.7-8.8 (6.5 ± 2.7)	3.8-12.6 (7.4 ± 2.2)	1.5-4.3 (2.9 ± 1.3)	3.0-8.0 (5.6 ± 1.7)

ing to the bone age, the BMD of children receiving single or multiple anticonvulsants did not differ significantly according to the medication period (less than 4 years vs more than 4 years)[12]. These results suggested that the bone age should be considered when assessing the BMD in children, although a study of the longitudinal changes in BMD in children receiving long-term anticonvulsant therapy had not yet been performed at that time.

In the present study, we used the DIP method to assess the longitudinal changes in BMD in children taking anticonvulsants and compared the results according to both chronological age and bone age. The present study may provide important information, as longitudinal BMD changes in children taking anticonvulsants for long periods have not, to our knowledge, been previously reported.

Material and Methods

The subjects of the investigation were 48 outpatients, consisting of 32 boys (aged 6 to 16 years) and 16 girls (aged 7 to 15 years) who were given a diagnosis of epilepsy (including febrile convulsions, in part), who regularly visited the Department of Pediatrics, Tokyo Women's Medical University Medical Center East. All the subjects had been taking anticonvulsants for over one year (1.4-12.3 years) and did not have any intellectual or motor disorders or any diseases affecting bone metabolism. Their serum drug concentrations were maintained at the optimum dosage. Informed consent was obtained from each patient's guardian.

In our previous cross-sectional study, the effects of various anticonvulsants on the BMD of 98 outpatients with epilepsy were evaluated[12]. In the present longitudinal study, 48 outpatients whose BMD had been examined several times at an interval of over 1 year before bone maturation had occurred were recruited. The number of subjects in the present study was approximately half of that in the former study mainly because of the longitudinal nature of the present study.

All the subjects were taking one or a combination of the following anticonvulsants: VPA, CBZ, and/or PB. The chronological age, duration of therapy, and age at the start of therapy of 4 groups determined according to the type of medication prescribed are listed in Table. The 4 groups consisted of 11 subjects (5 boys and 6 girls) receiving VPA alone, 19 subjects (13 boys and 6 girls) receiving CBZ alone, 5 subjects (3 boys and 2 girls) receiving PB alone, and 13 subjects (11 boys and 2 girls) receiving multiple anticonvulsants. In all the subjects, the drug levels of the anticonvulsants in the blood did not exceed the effective ranges, and good control of spasms was maintained.

To assess the BMD, an aluminum scale was placed on an X-ray film and an X-ray image of the left hand was obtained under conditions of a distance of 100 cm or more and 50 kV. The metacarpal X-ray images obtained using a television camera with transmitted illumination were analyzed using high-resolution image-processing equipment (Bone Analyzer DIP-1000; Hamamatsu Photonics Inc., Hamamatsu, Japan). For about 10% of the central part of the 2nd metacarpal of the left hand, the bone concentration pattern was obtained in a width of 6-8 mm, or 30-40 lines, by measuring the picture luminance relative to the aluminum scale and equalized. The obtained indices were the average bone density per bone width ($\Delta GS/D$), which is equivalent to

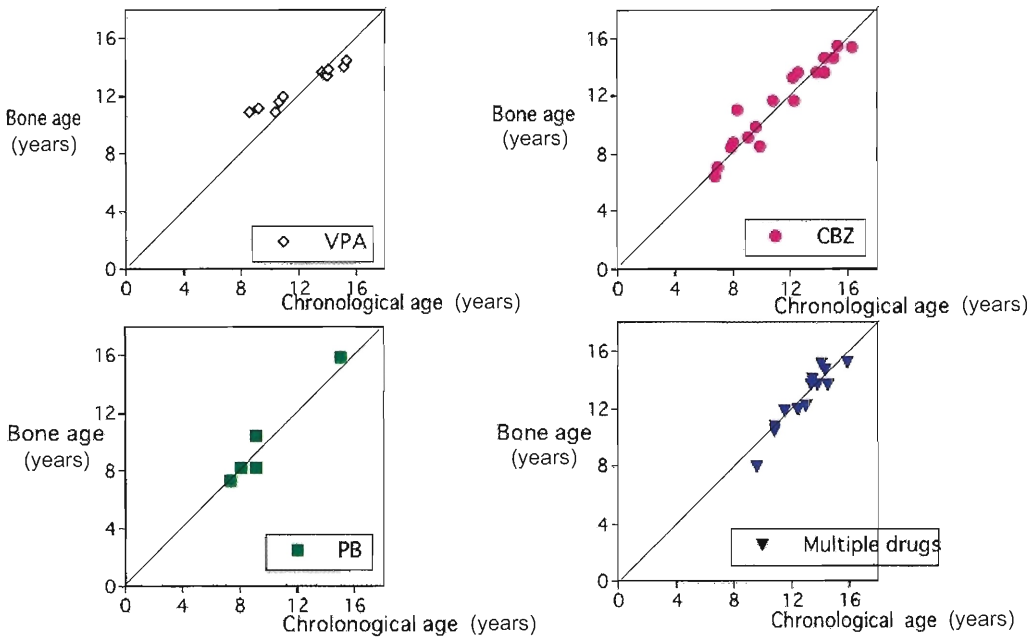

Fig. 1 Correlation between chronological age and bone age in each subject according to medication type.
No remarkable delays or accelerations in bone age were observed among children receiving anticonvulsants.

the BMD, and the bone cortical width index per bone width (MCI).

To assess the bone age, the bone maturation scores for the radius-ulna-short bones (RUS) were calculated using the Tanner-Whitehouse 2 methods[13] and the same film that was used to measure the BMD using the DIP method. The bone age was determined based on the standard Japanese bone maturation scores[13].

In each subject, the SD (standard deviation) scores for the chronological and bone ages were calculated using the mean BMD according to sex and age and the SD of the BMD according to sex and age in Japanese children[14]. The SD scores for the chronological and bone ages were calculated by subtracting the mean BMD according to sex and age from each of the measured BMD values and then dividing the result by the SD. The difference in the SD score for the BMD at 2 periods during treatment, the ΔSD score of the BMD per year (ΔBMD-SDS/year), was calculated for each subject and evaluated.

For the statistical analysis, the Spearman rank correlation coefficient, simple linear regression, Wilcoxon test, Mann-Whitney test, and Kruskal-Wallis test were used. For all the statistical tests, significance was defined as $P<0.05$.

Results

1. Correlation between chronological age and bone age

The correlation between the chronological age and the bone age in each subject was evaluated using the latest data regarding the type of medication: VPA, CBZ, PB, or multiple drugs. In all the groups, statistically close correlations were recognized between the chronological age and the bone age. These results indicated that no remarkable delay or acceleration in bone age was noted among the children receiving anticonvulsants.

2. Assessment of changes in BMD according to chronological age

Fig. 2 shows the changes in the SD score for the BMD of each subject according to chronological age. In most patients, the SD scores for the BMD in patients under 11 years of age were higher than zero. In all the subjects, the SD score for the BMD showed a downward tendency that was statistically significant after 11 years of age, whereas the SD

score for the BMD showed no significant changes before 11 years of age.

Fig. 3 shows the changes in the SD score for the BMD per year (ΔBMD-SDS/year) for each subject according to chronological age. A significant negative correlation between the ΔBMD-SDS/year and the duration of therapy (years) was observed in the groups treated with VPA ($y = -0.076x + 0.172$, $r = 0.766$, $P < 0.01$), CBZ ($y = -0.104x + 0.550$, $r = 0.463$, $P < 0.05$), or multiple drugs ($y = -0.118x + 0.534$, $r = 0.717$, $P < 0.01$). These results indicated that physiological increases in the BMD were impaired in children treated with anticonvulsants, compared with normal children, in a manner that depended on the duration of therapy. A significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy (years of age)was observed in only the group treated with multiple drugs ($y = 0.112x - 0.960$, $r = 0.615$, $P < 0.05$). These results suggested that the rate of increase in the BMD tended to become smaller when therapy was started at an earlier age.

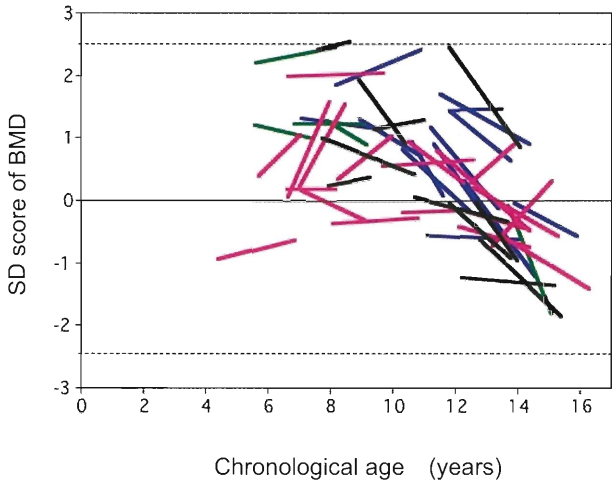

Fig. 2 Change in the SD score of the BMD in each subject according to chronological age.
The black lines show patients treated with VPA (n = 11), the red lines show patients treated with CBZ (n = 19), the green lines show patients treated with PB (n = 5), and the blue lines show patients treated with multiple drugs (n = 13). In all subjects, the change in the SD score of the BMD decreased remarkable after 11 years of age, compared with before 11 years of age.

3. Assessment of changes in BMD according to bone age

Fig. 4 shows the changes in the SD score for the BMD for each subject according to the bone age. In some subjects treated with anticonvulsants, the SD

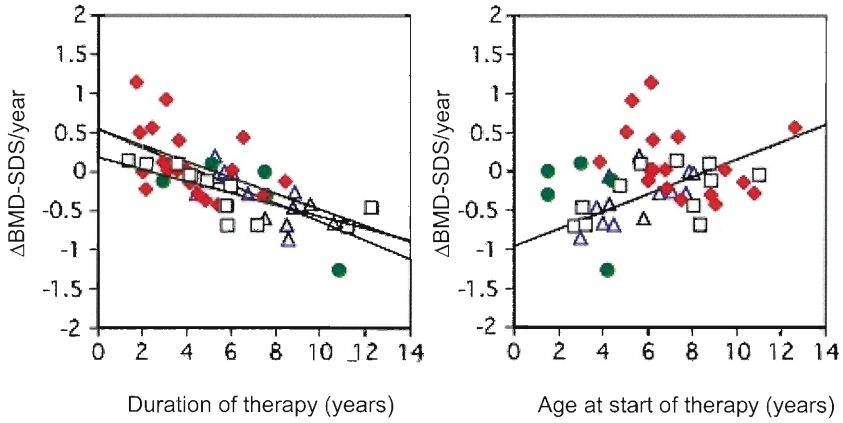

Fig. 3 Correlation between change in the SD score of the BMD per year (ΔBMD-SDS/year) according to chronological age and the duration of therapy or the age at the start of therapy.
A significant negative correlation between the ΔBMD-SDS/year and the duration of therapy (years) was observed in 3 groups: those treated with VPA (□) ($y = -0.076x + 0.172$, $r = 0.766$, $P < 0.01$), those treated with CBZ (◆) ($y = -0.104x + 0.550$, $r = 0.463$, $P < 0.05$), and those treated with multiple drugs (△) ($y = -0.118x + 0.534$, $r = 0.717$, $P < 0.01$). A significant negative correlation was not seen in the group treated with PB (●). A significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy was found only in the group that was treated with multiple drugs (△) ($y = 0.112x - 0.960$, $r = 0.615$, $P < 0.05$).

score for the BMD showed a downward tendency, while an upward tendency was seen in other subjects without any correlation with the bone age. We compared two groups, subjects with a bone age of less than 11 years and subjects with a bone age equal to greater than 11 years. No significant correlation was observed between these two groups. Fig. 5 shows the ΔBMD-SDS/year for each subject according to the bone age. A tendency toward a negative correlation between the ΔBMD-SDS/year and the duration of therapy (years) was only observed in the group treated with PB ($y = -0.204x + 1.219$, $r = 0.866$, $P < 0.1$). No significant correlation between the ΔBMD-SDS/year and the age at the start of therapy (years of age) was observed in any of the groups.

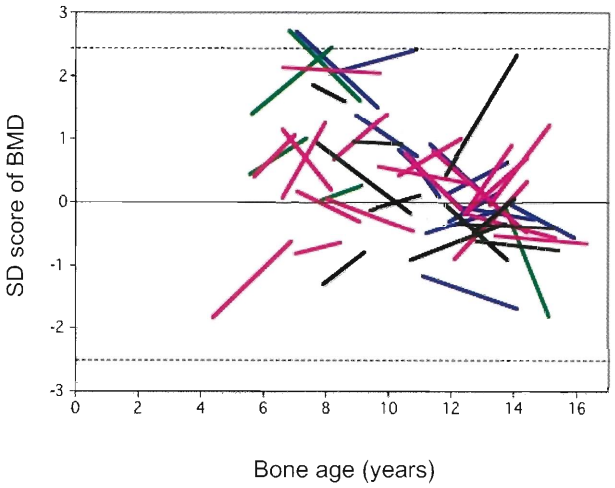

Fig. 4 Change in the SD score of the BMD in each subject according to bone age.
The black lines show the patients treated with VPA (n = 11), the red lines show the patients treated with CBZ (n = 19), the green lines show the patients treated with PB (n = 5), and the blue lines show the patients treated with multiple drugs (n = 13). In some of the subjects, the change in the SD score of the BMD showed a downward tendency, while an upward tendency was seen in others without any correlation with bone age.

Discussion

The present study is the first report, to our knowledge, to use the DIP method to assess longitudinal changes in the BMD in children taking anticonvulsants and to compare the results according to both chronological age and bone age.

Recently, dual-energy X-ray absorptiometry (DXA method) has been used to measure the BMD in the lumbar spine region, and this method has been useful for the early diagnosis of osteoporosis[15]. However, the DXA method is not convenient for use in children who are very young or who have mental development delays, as it requires both a lengthy time and anesthesia to perform. The correlations between measurements obtained using each method have been previously studied, and the use

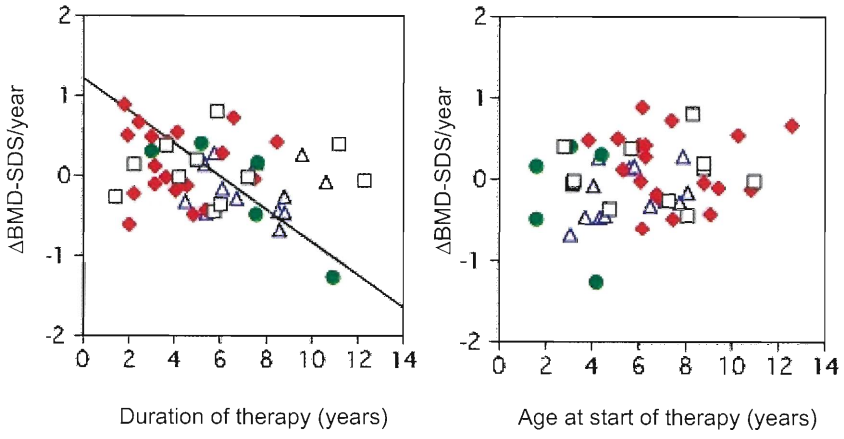

Fig. 5 Correlation between the ΔBMD-SDS/year according to bone age and the duration of therapy or the age at the start of therapy.
A negative but not significant correlation between the ΔBMD-SDS/year and the duration of therapy (years) was observed only in the group treated with PB (●) ($y = -0.204x + 1.219$, $r = 0.866$, $P < 0.1$), and not in the groups treated with VPA (□), CBZ (◆), or multiple drugs (△). No significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy was observed in any of the groups.

of the DIP method to measure the BMD of the metacarpal bones has been confirmed to be especially useful because this measurement is easy to perform and the results are also significantly correlated with those obtained using the DXA method[16]. Numerous studies have examined anticonvulsants and bone metabolic disorders. In these studies, a decrease in the BMD was observed only in cortical bone or was initially recognized in cortical bone[17]. Consequently, the DIP method was used in the present study.

Human bone structures consist of cancellous bone and cortical bone. Cancellous bone is more sensitive to pharmacologically induced reductions in bone minerals, while cortical bone comprises about 80% of human bone structures and its bone mineral content accurately reflects calcium metabolism in the whole body. Calcium metabolism is influenced not only by food intake and absorption from the digestive tract, but also by endocrinological metabolic factors, such as vitamin D and parathyroid hormone, exposure to sunlight, exercise, and physical activity. In the present study, the subjects had neither intellectual disabilities nor physical handicaps, which can otherwise affect bone metabolism.

In normal children, the BMD is known to increase rapidly in a biphasic manner during adolescence in both boys and girls, with a growth spurt starting at about 12 years of age in boys and 10 years of age in girls[11]. The correlations between BMD and chronological age and between BMD and bone age were similar before adolescence, but during adolescence the correlation between BMD and bone age was stronger than that between BMD and chronological age. Using the computed X-ray densitometry (CXD) method, Sato et al. reported that both the average bone density per unit bone width (ΔGS/D) and the bone cortical width index (MCI) in the 2nd metacarpal bone of the left hand showed an upward tendency until adulthood, and the ΔGS/D in particular showed a significant increase at 14 years in girls and at 16 years in boys[18]. Osamura et al. reported the whole body amounts of bone minerals in healthy children using the DXA method and found that the BMD of the whole body was strongly correlated with the chronological age in boys and girls and increased in a linear manner[19]. Matkovic et al. reported that the BMD of the 2nd-4th lumbar vertebrae and the distal one-third of the radial bone increased linearly up to an age of 19 years[20].

We tried to examine the longitudinal changes in the BMD in individual subjects taking anticonvulsants and assessed the change in the SD score of the BMD as the increasing rate for one year (ΔBMD-SDS/year). We demonstrated that in all the subjects, the SD score for the BMD showed a downward tendency that was statistically significant after 11 years of age, while the SD score for the BMD showed no significant change before 11 years of age (Fig. 2). This result suggested that anticonvulsants significantly suppress the rate of BMD increase during adolescence. However, the numbers of subjects examined both before and after 11 years of age was limited, and further study may be needed.

When assessing the chronological age, a significant negative correlation between the ΔBMD-SDS/year and the duration of therapy was observed in the groups receiving VPA monotherapy, CBZ monotherapy, and multiple drugs (Fig. 3). This result suggested that longer medication periods of anticonvulsants suppressed the rate of BMD increase, compared with the rate in normal children. In addition, in subjects treated with multiple drugs, a significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy was observed (Fig. 3). On the other hand, when assessed for bone age, a negative but not significant correlation between the ΔBMD-SDS/year and the duration of therapy was observed only in children treated with PB, and no significant positive correlation between the ΔBMD-SDS/year and the age at the start of therapy was observed in any of the groups (Fig. 5). These results suggest that anticonvulsants may affect bone age. The longitudinal changes in bone age in each treatment group were analyzed, but the individual variations in the change in bone age were remarkable and the subject number was too small to assess the correlation between bone age and the effects of anticonvulsants among the

four treatment groups.

In terms of studying the effects of anticonvulsants on the BMD, Otsubo reported that the %MCI value was lowest in a group that had been receiving medication for three years, reaching a healthy child's level after five to six years and decreasing remarkably after long-term administration[3]. Furthermore, he reported that the most important factor affecting the BMD was the age at the start of therapy. Osamura et al. reported that the BMD of the whole body, as measured using the DXA method, was higher in subjects receiving a single anticonvulsant than in control subjects during the early stages of treatment (before 34.2 months) but subsequently decreased (after 34.2 months), suggesting the possibility of a compensatory mechanism in the body, although the exact mechanism was unknown[4]. It should be noted that a study of adult epilepsy patients showed no correlation between the age at the start of therapy and abnormalities in bone mineral levels, suggesting that the effect of age at the start of therapy may be unique to childhood[5]. In the present study, the difference between the results for ΔBMD-SDS/year assessed according to the chronological age and assessed according to the bone age may be due to a delay or acceleration of the bone age in each subject during treatment with the anticonvulsants.

Different effects of different medicines, such as PB, CBZ, and VPA, have also been reported. Yamada used the CXD method to examine children and reported that 11.9% of the subjects exhibited a reduction in BMD, especially in children who were over 10 years old, who were over 4 years old at the start of treatment, who had received medication for over 7 years, and who were receiving PB as an anticonvulsant, suggesting the presence of different bone reactivities to drugs depending on the age of the subject[6]. Sheth et al. investigated the amount of bone mineral in the 2nd-4th lumbar vertebrae and the distal one-third of the radial bone using the DXA method in 26 children (6-20 years old) with idiopathic epilepsy who were treated with CBZ or VPA monotherapy and in 27 healthy children. Although the healthy control subjects showed a linear increase in both regions, the children treated with CBZ showed a reduction of 5% or less in the amount of bone mineral. On the other hand, children treated with VPA showed significant reductions of 14% of the amount of bone mineral at the 2nd-4th lumbar vertebrae and 10% at the distal one-third of the radial bone ($P = 0.003$)[7]. Chung et al. measured the BMD using the DXA method for 2 to 15-year-old children and reported that the BMD of the rib and the backbone decreased in children receiving PB or PHT for 24 months or more, compared with the values in a normal control group[8].

Our results suggest that anticonvulsants therapy may induce a reduction in the rate of BMD increase, especially during adolescence, in subjects receiving medication for long time periods. However, conventional evaluations based only on chronological age may result in an overestimation of the effects of anticonvulsants on the BMD, considering that the BMD of normal children is similarly correlated with chronological age and with bone age before adolescence but is strongly correlated with bone age but not with chronological age during adolescence. If the maximum BMD remains at a low value during the growth phase in childhood, the subject may develop osteoporosis at an early stage in the future, and close attention may be required when medical treatment with anticonvulsants is continued in these subjects. For subjects who exhibit a reduction in BMD, especially before or during adolescence, a precise follow-up of the BMD is needed not only according to the chronological age, but also according to the bone age, which indicates the biological growth process in individual subjects much more accurately.

Conclusion

Anticonvulsants therapy may reduce the rate of BMD increase, especially during adolescence, in patients who receive medication for long time periods. A precise follow-up of the BMD is needed not only according to the chronological age, but also according to the bone age, which reflects the biological growth process much more accurately, especially during adolescence.

Conflicts of interest

The authors have no conflicts of interest to report.

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抗けいれん剤内服中の児の縦断的骨塩量の評価

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抗けいれん剤内服中の個々の小児例における骨密度の縦断的データの検討は報告されていない．我々は骨密度の経時的変化をDIP（digital image processing）法を用いて，服薬期間と治療開始年齢から縦断的に，同時に暦年齢，骨年齢との比較を含め検討した．対象は東京女子医科大学東医療センター小児科外来に通院し，抗けいれん剤のバルプロ酸ナトリウム（VPA）・カルバマゼピン（CBZ）・フェノバルビタール（PB）の単剤投与もしくは多剤併用療法による治療を受けた外来てんかん患児48人（6～16歳）である．いずれも知能障害や運動能力に制限を持たず，骨代謝に影響を及ぼす他疾患の合併は認められない．全例に検査内容と目的を説明し，保護者の同意を得て検査を施行した．正常小児の骨密度の基準値を用い，各人の暦年齢，骨年齢よりそれぞれ標準偏差(SD)を算出し，経時的変化を年単位の変化（ΔBMD-SDS/year）として評価し，薬剤別に服薬期間，服薬開始年齢より比較検討した．暦年齢より求めた骨密度のSDの経時的変化は，全ての薬剤において11歳以後に顕著な減少傾向を認めた．暦年齢より算出したΔBMD-SDS/yearは，多剤併用療法のグループにおいてのみ治療開始年齢と有意な相関を認めた．しかしながら，骨年齢より算出した骨密度の年単位の変化は，どのグループにおいても有意な相関は認めなかった．抗けいれん剤を服薬している児では，服薬期間が長くなるほど，特に思春期において骨密度の増加率の減少を引き起こす．正確な骨密度の経時的変化には，暦年齢のみではなく，特に思春期前および思春期においてより厳密な生物学的成長過程を反映する骨年齢による骨密度の評価が必要とされる．