The effect of anticonvulsant use on bone mineral density in non-ambulatory children with cerebral palsy

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ABSTRACT

Introduction: Studies showed that use of anticonvulsants (antiepileptic drugs) might be associated with reduced bone mineral density. The primary objective of this study was to evaluate the effect of anticonvulsants on bone mineral density in non-ambulatory children with cerebral palsy. The secondary objective was to identify their risk factors for low bone mineral density.

Methods: This case series with internal comparisons was conducted in a paediatric residential rehabilitation centre in Hong Kong. Overall, 32 patients were enrolled. The study group comprised 18 patients (6 males, 12 females) aged 5.0 to 19.5 years (mean ± standard deviation, 13.8 ± 4.7 years); all were prescribed anticonvulsant therapy for more than 2 years. The comparison group comprised 14 patients (6 males, 8 females) aged 7.0 to 19.1 years (mean, 16.4 ± 3.0 years) who were concomitant non-ambulatory residents with cerebral palsy and were not prescribed any anticonvulsant therapy prior to study recruitment. Patients underwent a physical examination, blood tests, nutritional assessment, and dual-energy X-ray absorptiometry scan of the total body less head. Z-scores were calculated.

Results: There was no significant difference in Z-scores of total body less head between groups. Among children with low bone mineral density (Z-scores ≤ -2.0) and normal bone mineral density, multivariate analysis revealed that higher weight-for-age Z-score (adjusted odds ratio=0.015) and presence of puberty (adjusted odds ratio=0.027) were independent factors for bone mineral density improvement. Hosmer-Lemeshow goodness of fit test (P=0.315) was not significant. Nagelkerke R^2 was 0.677, signifying a relatively well-fitting model.

Conclusion: There was no evidence that anticonvulsant therapy has any detrimental effect on bone mineral density in non-ambulatory children with cerebral palsy. A low weight-for-age Z-score was associated with low bone mineral density. Early nutritional intervention to optimise body weight may help to increase bone mineral density.

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New knowledge added by this study
- Anticonvulsant use shows no significant and detrimental impact on bone mineral density (BMD) of non-ambulatory cerebral palsy children.
- A low weight-for-age Z-score was found to be a significant independent risk factor predictive of low BMD.

Implications for clinical practice or policy
- Optimal pharmacological treatment for epilepsy control can be pursued without jeopardising bone mineralisation in non-ambulatory cerebral palsy children.
- Optimising nutritional status in this group of children is important in improving bone mineralisation and thus decreasing pathological fracture.

Introduction

Osteoporosis is a skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue that results in compromised bone strength and a predisposition to fracture.[1] Childhood and adolescence are critical periods for bone mineralisation. Peak bone mineral density (BMD) achieved by early adulthood determines the risk of pathological fracture. Bone mass can be objectively measured by BMD and is correlated with risk of osteoporotic fracture.[2]

Dual-energy X-ray absorptiometry (DXA) scanning enables cost-effective quantitative measurement of BMD. Such methodology is the gold

standard because it can detect bone mineral loss of 2% to 5%. Abnormal homeostasis of vitamin D, calcium, and phosphorous may lead to imbalanced osteoclastic and osteoblastic dynamics that will result in osteopenia and even osteoporosis. There have been reports from large- and small-scale studies of problems in bone mineralisation and vitamin D or calcium metabolism in patients with cerebral palsy (CP).[3,4] Dietary restrictions, oromotor dysfunction, malabsorption, and limited sunlight exposure may lead to poor nutrition, low calcium intake, or altered vitamin D metabolism. These in turn contribute to poor mineralisation. Limited weight-bearing during the period of skeletal growth may also lead to reduced BMD. Chronic therapy with anti-epileptic drugs (AEDs) may cause hypocalcaemia, hypophosphataemia, raised serum alkaline phosphatase, elevated serum parathyroid hormone, reduced biologically active vitamin D metabolites, rickets, and osteomalacia. The mechanism is unclear, however.[5]

A study revealed that AED use was associated with reduced BMD in 35 pairs of twin adults, and the effect was more marked in those prescribed enzyme-inducing AEDs, for example, phenytoin and phenobarbitone.[6] A decrease in BMD (in g/cm^2) of 6.4% and 4.6% at the lumbar spine and femoral neck respectively in their twin control pair was detected. For valproate, the effect was not consistently demonstrated.[7,8]

Chronic treatment with AEDs was observed to be significantly correlated with a lower BMD in 96 ambulatory children and young adults with epilepsy with a mean Z-score of -1.23 compared with 0.16 of a control group.[9] In our retrospective study of 109 CP children in 2006, however, we could not demonstrate any association of AEDs with increased fracture rate in non-ambulatory CP children.[10] In children with CP and a Gross Motor Function Classification System (GMFCS) level of 4 to 5 (bed-bound), the possible impact of anticonvulsants on BMD was not clearly demonstrated.

The primary objective of this study was to evaluate the effect of AEDs on BMD in non-ambulatory children with CP. The secondary objective was to identify the risk factors for low BMD in this group of children.

Methods
Subjects
Patients at the Developmental Disabilities Unit (DDU) of Caritas Medical Centre, Hong Kong were enrolled in the study from 1 October 2012 to 30 September 2013. The DDU is the largest long-term care facility for children with severe developmental disabilities and special health care needs in Hong Kong. Among the 100 residents, over 90% were non-ambulatory and over 50% had CP.

抗癲癇藥物對臥床的小兒腦癱患者骨密度的影響

鄭斯穎、高震雄、李靜賢

引言：研究顯示使用抗癲癇藥物可能與骨密度下降相關。本研究主要評估抗癲癇藥物對於臥床的小兒腦癱患者骨密度的作用，其次找出引致患者低骨密度的危險因素。

方法：這個具內部比較的病例系列於香港一所兒科寄宿康復中心內進行。研究對象為32名患者。實驗組有18例（6男12女），年齡介乎5.0至19.5歲（平均年齡13.8歲，標準差4.7歲）。他們均已接受抗癲癇治療超過兩年。對照組有14例（6男8女），年齡介乎7.0至19.1歲（平均年齡16.4歲，標準差3.0歲），他們同樣是臥床的小兒腦癱患者，但在研究前並無接受任何抗癲癇治療。所有患者接受身體檢查、驗血、營養評估，以及不包括頭部的全身雙能X線骨密度掃描，並計算其Z值。

結果：兩組間不包括頭部的全身雙能X線骨密度掃描的Z值無顯著差異。多變量分析顯示在低骨密度（Z值≤-2.0）和正常骨密度的患者中，較高的按年齡體重的Z值（調整後比值比=0.015）和進入青春期與否（調整後比值比=0.027）為骨密度改善的獨立因素。Hosmer-Lemeshow擬合優度並不顯著（P=0.315）。Nagelkerke R^{2}為0.677，顯示模型對擬合度較好。

結論：沒有證據顯示抗癲癇藥物對臥床的小兒腦癱患者骨密度有不良影響。按年齡體重的Z值低與低骨質密度有關。及早作營養干預來優化體重可能有助患者增加骨密度。

The inclusion criteria in this study were: (1) children and adolescents aged between 5 and 19 years; (2) GMFCS level 4 or 5; (3) the presence of spastic or mixed spastic dyskinetic CP; and (4) prescribed AED for more than 2 years.

The control group without anticonvulsant therapy comprised concomitant non-ambulatory DDU residents with CP who were not prescribed AEDs for more than 2 years prior to recruitment to the study.

The exclusion criteria included (1) GMFCS level of 1 to 3; (2) patients with underlying hepatic or renal disease; (3) presence of disease primarily involving bone metabolism or a family history of bone metabolic disorders; (4) known thyroid or parathyroid disease; (5) history of pathological long bone fracture; (6) history of chronic diarrhoea or malabsorption; (7) long-term intake of the following medications: non-physiological dose of glucocorticoid, anabolic steroid, vitamin A, non-steroidal anti-inflammatory drugs, bisphosphonates, thiazide diuretics, or calcitonin.

Sample size estimation
Coppola et al[9] reported a mean BMD Z-score of -1.23 and 0.16 in 96 ambulatory epileptic patients and 63 controls, respectively. In 2012, the same group showed the mean Z-score to be -1.69 (n=47)

and -0.83 (n=40) respectively in mentally retarded children with CP, with and without epilepsy.[11] Based on these findings, we proposed a difference in Z-score of ≥1 to indicate a clinically significant reduction in BMD. In order to detect a Z-score difference of 1 with power of 0.8, 16 subjects were recruited in each group.[12]

Data collection and determination of bone mineral density

Upon entry, data were collected for age, gender, body weight, body height, body mass index (BMI), presence of contractures, skinfold thickness (triceps, lower biceps, and subscapular), and pubertal stage according to Tanner's classification. Weight-for-age Z-score was calculated based on referenced data from a 1993 territory-wide growth survey of Hong Kong children.[13] Blood taking was performed on the same day of DXA scan to evaluate calcium, phosphorous, alkaline phosphatase, transaminase, total protein, urea, creatinine, serum osmolality, and total cell count. A spot urine calcium-to-creatinine ratio (mmol/mmol) and urine calcium-to-osmolality ratio (mg/L:mosmo/kg) was also determined on the same day. Current dietary information was reviewed and daily calcium and vitamin D content were calculated by a dietitian.

In this study, BMD was determined by DXA of total body less head (TBLH) using a Lunar Prodigy Advance DXA bone densitometer (GE Healthcare, Madison [WI], US) with the latest Chinese children total BMD database installed.[14,15] All subjects had BMD measured by the same validated densitometer to eliminate measurement error. Individual BMD value was expressed as g/cm^2 and Z-score. Z-score is the number of standard deviations of the patient's BMD above or below the average age- and sex-matched reference value. For the paediatric age-group, the current definition for osteoporosis includes BMD Z-score of ≤−2.0 adjusted for age, gender, and body size plus a clinically significant fracture defined in the International Society for Clinical Densitometry (ISCD) 2007 official positions.[16] The head is disproportionately large in young children and may mask deficits at other skeletal sites, thus TBLH (subtotal/TBLH) BMD, which was recommended by ISCD 2007 official positions for the evaluation of child's bone health, was used in this study. For children with CP, TBLH BMD is more feasible and provides a holistic picture for BMD estimation.

Statistical analyses

Effect of antiepileptic drugs on bone mineral density in non-ambulatory children with cerebral palsy

In bivariate analysis, normally and non-normally distributed data were analysed by independent sample *t* tests and Mann-Whitney *U* tests, respectively. Categorical data were compared using Chi squared and Fisher's exact tests. Clinically relevant covariates (presence of puberty, daily calcium intake, and number of AED use) and the covariate (weight-for-age Z-score) approaching statistical significance (P<0.05) in bivariate analysis were entered into multivariable analysis (Enter Method). Statistical significance was defined as two-tailed probability below 0.05.

Risk factors for low bone mineral density in non-ambulatory children with cerebral palsy

Data of TBLH were split into low-BMD group versus normal-BMD group—those with TBLH Z-score of ≤−2.0 were considered to have low BMD. Baseline characteristics of the low- and normal-BMD groups were compared. Multivariable logistic regression analysis was used to examine the independent effect of puberty, weight-for-age Z-score (gender adjusted), number of AEDs, and daily calcium intake on TBLH Z-score.

All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US).

The study was approved by the Ethics Committee of Kowloon West Cluster of Hospital Authority, Hong Kong. Informed consent was obtained from respective parents or the legal guardians from the Social Welfare Department, Government of the Hong Kong Special Administrative Region.

Results
Effect of antiepileptic drugs on bone mineral density in non-ambulatory children with cerebral palsy

The subjects were enrolled from 1 October 2012 to 30 September 2013 in DDU. Sixty-two children with CP aged 5 to 19 years were identified. Informed consent was obtained from a legal guardian for 44 patients of whom 12 were excluded from study—four had a history of fracture, two had severe deformity making DXA technically difficult, one had poorly controlled asthma and required long-term steroid therapy, and five had deranged liver or renal function. Of the remaining 32 children and adolescents, 18 (6 males, 12 females) aged 5.0 to 19.5 (mean ± standard deviation, 13.8 ± 4.7) years comprised the study group. The control group consisted of 14 children and adolescents (6 males, 8 females) aged 7.0 to 19.1 (mean, 16.4 ± 3.0) years.

Among the 18 subjects in the study group, eight were prescribed one AED and 10 were prescribed two or more. Sodium valproate was prescribed to eight children, carbamazepine to three, topiramate to three, phenobarbitone to five, phenytoin to one, and lamotrigine to four. In view of the limited population

size, the impact of individual anticonvulsants was not analysed.

The two groups showed no significant difference in age, gender, BMI, weight-for-age Z-score, CP type, daily calcium intake, or daily vitamin D intake (Table 1).

Twelve (67%) patients in the study group were in puberty, compared with 13 (93%) patients in the control group (P=0.104). Sixteen (89%) patients in the study group were tube feeders compared with four (29%) in the control group (P=0.001). Among the oral feeders, all were reported by their caretaker to have a satisfactory dietary intake. Mean weight-for-age Z-score showed no significant difference between the study and control groups (P=0.226) [Table 1]. There was also no significant difference in the TBLH Z-scores (P=0.989; Table 1) or biochemical parameters of bone metabolism between the two groups (Table 2).

Low BMD was defined as TBLH Z-score of ≤−2.0 and was evident in 18 (56%) patients. When comparing groups with low and normal BMD, there was no significant difference on univariate analysis in gender, age, CP, BMI, feeding mode, use of AEDs, puberty, or daily calcium and vitamin D intake (Table 3). Weight-for-age Z-score was significantly

TABLE 1. Comparison of clinical characteristics and TBLH Z-score in children prescribed anticonvulsants (study group) and those not (control group)

Characteristic / TBLH Z-score	Data*		P value
	Study group (n=18)	Control group (n=14)	
Female:male	12:6	8:6	0.581
Mean age (years)	13.8 (5.0 to 19.5)	16.4 (7.0 to 19.1)	0.065
BMI (kg/m²)	16.8 (11.0 to 22.8)	16.6 (12.8 to 25.9)	0.907
Weight-for-age Z-score	-1.70 (-3.19 to -1.12)	-2.25 (-3.80 to -0.82)	0.226
Cerebral palsy			
Spastic	8 (44)	7 (50)	0.755
Dyskinetic/mixed	10 (56)	7 (50)	
Puberty	12 (67)	13 (93)	0.104
Prepubertal	6 (33)	1 (7)	
Feeding practice			
Tube feeding	16 (89)	4 (29)	0.001†
Oral feeding	2 (11)	10 (71)	
Daily calcium intake (mg)	1067 ± 362.4	1210 ± 526.4	0.371
Daily vitamin D intake (IU)	564 ± 260.5	609 ± 396.3	0.702
TBLH Z-score	-2.44 (-4.6 to -0.3)	-2.55 (-3.8 to -1.2)	0.989

Abbreviations: BMI = body mass index; TBLH = total body less head
* Data are shown as No., No. (%), mean (range), or mean ± standard deviation
† Fisher's exact test

TABLE 2. Comparison of biochemical parameters of bone metabolism in children prescribed anticonvulsants (study group) and those not (control group)

Biochemical parameter	Mean (range)		P value‡
	Study group (n=18)	Control group (n=14)	
Alkaline phosphatase (U/L)	136.8 (59-232)	133.4 (71-217)	0.856
Calcium (mmol/L)	2.30 (2.14-2.44)	2.33 (2.14-2.43)	0.246
Phosphate (mmol/L)	1.24 (0.92-1.71)	1.37 (1.01-1.83)	0.140
Urine test			
Calcium-to-creatinine ratio (mmol/mmol)*	0.36 (0.09-0.87)	0.41 (0.1-0.69)	0.499
Calcium-to-osmolality ratio (mg/L/mosmo/kg)†	0.19 (0.07-0.43)	0.19 (0.05-0.43)	0.925

* Value >0.7 denotes hypercalciuria
† It is more accurate in patients with reduced muscle mass, value >0.25 denotes hypercalciuria
‡ Independent sample t tests

TABLE 3. Comparison of clinical characteristics and use of anticonvulsants between children with low and normal BMD

Characteristic / use of anticonvulsants	Data*		P value
	Low-BMD group (n=18)	Normal-BMD group (n=14)	
Female:male	9:9	11:3	0.098
Age (years)	16.0 (7.0 to 19.5)	13.6 (5.0 to 19.1)	0.138
BMI (kg/m²)	16.41 (12.52 to 22.76)	17.10 (11.00 to 25.94)	0.544
Weight-for-age Z-score	-2.57 (-3.80 to -1.07)	-1.12 (-2.44 to -1.12)	0.001
Cerebral palsy			
Spastic	9 (50%)	6 (43%)	0.668
Dyskinetic / mixed	9 (50%)	8 (57%)	
Puberty	15 (83%)	10 (71%)	0.669
Prepubertal	3 (17%)	4 (29%)	
Feeding practice			
Tube feeding	12 (67%)	8 (57%)	0.581
Oral feeding	6 (33%)	6 (43%)	
Daily calcium intake (mg)	1208 ± 393	1027 ± 484	0.257
Daily vitamin D intake (IU)	637 ± 276	515 ± 372	0.297
Anticonvulsant use	9 (50%)	9 (64%)	0.721
Monotherapy	4	4	
≥2 Anticonvulsants	5	5	
Calcium-to-osmolality ratio (mg/L/mosmo/kg)	0.20 ± 0.08	0.18 ± 0.11	0.59

Abbreviations: BMD = bone mineral density; BMI = body mass index
* Data are shown as No., No. (%), mean (range), or mean ± standard deviation

TABLE 4. Multivariate analysis of potential factors affecting TBLH BMD Z-score*

Covariate	Adjusted OR	95% CI	P value
Puberty	0.027	0.001-0.948	0.047
Weight-for-age Z-score	0.015	0.001-0.390	0.012
No. of anticonvulsants used	0.594	0.163-2.165	0.430
Daily calcium intake	0.997	0.993-1.000	0.063

Abbreviations: BMD = bone mineral density; CI = confidence interval; OR = odds ratio; TBLH = total body less head
* Hosmer-Lemeshow goodness of fit test (P=0.315); Nagelkerke R^2=0.677

lower (-2.57 vs -1.12; P=0.001) in the low BMD group (Table 3).

When covariates including weight-for-age Z-score, presence of puberty, daily calcium intake, and number of AEDs used were analysed by multiple logistic regression, higher weight-for-age Z-score (adjusted odds ratio [OR]=0.015; 95% confidence interval [CI], 0.001-0.390) and presence of puberty (adjusted OR=0.027; 95% CI, 0.001-0.948) remained significant independent predictors for occurrence of a relatively normal BMD (ie TBLH Z-score >2.0). Hosmer-Lemeshow goodness of fit test (P=0.315) was non-significant, indicating a model prediction that was not significantly different to observed values. Nagelkerke R^2 was 0.677, again signifying a relatively well-fitting model (Table 4).

Discussion

In the present study, DXA evaluation in non-ambulatory children with CP, with or without AED use, revealed a low BMD in 56% of those who underwent DXA. This is concordant with the findings in previous studies[4,17-19] with prevalence of low BMD ranging from 27% to 77%. Low BMD is the proximate cause of low-energy fracture in this group of children. Other factors such as stiff joints, poor balance leading to falls, and violent seizures may also contribute. Nearly 20% of such children have sustained a femoral fracture at some point.[20]

The impact of AED on BMD was unclear in non-ambulatory children with CP. The physician often faces a dilemma in optimising anticonvulsant treatment in this group of children who are already at high risk of developing osteoporotic long bone fracture.

Early studies revealed that treatment with enzyme-inducing anticonvulsants—for example, phenytoin and phenobarbitone—may induce catabolism of 25-hydroxyvitamin D, leading to rickets.[21,22] Recent research on the effect of AED on BMD is inconclusive, and the results are often

confounded by methodological flaws. In a cross-sectional study, Farhat et al[5] measured the BMD in 71 ambulatory subjects who were prescribed AED for more than 6 months. Reduced BMD was found in adults (n=42) but not children (n=29). There was no control group and the findings were only compared with paediatric data from the manufacturer, rendering it difficult to detect any small but significant difference secondary to AED treatment. Ecevit et al[23] measured femoral neck BMD in 31 healthy children and 33 subjects with idiopathic epilepsy treated with either carbamazepine (n=17) or valproate (n=16). Valproate but not carbamazepine monotherapy was associated with a significant reduction in BMD. In this study, however, more children had attained puberty in the control group (n=13, 93%) than in the AED group (n=12, 67%), which may have confounded the results. Coppola et al[9] compared the BMD of 96 children with epilepsy alone or in association with CP and/or mental retardation against a control group of 63 healthy ambulatory subjects. While univariate analysis illustrated a reduced BMD Z-score in the AED group, no difference was found after adjustment for ambulatory status, mental retardation, lack of physical activity, and BMI in multivariate analysis.

In this study, we focused on non-ambulatory children with CP and severe mental retardation. This is the population most vulnerable to pathological long bone fracture, with a lifetime risk estimated to be 20%. This group of children is also prone to develop refractory epilepsy that requires multiple AEDs at high doses. By recruiting concomitant residents from the same facility as the control group, we minimised the confounding effect of factors that may contribute to low BMD, namely ambulatory status, physical activity, and nutritional status. Our findings support that long-term use of AED in this group of children does not have any significant adverse effect on BMD. Optimal pharmacological treatment can be pursued without jeopardising bone mineralisation.

In multivariable analysis, there was a significant association of BMD Z-score with the presence of puberty. This may be due to the physiology and time frame for bone mineralisation that surges in puberty and reaches a peak at 20 years of age. Variation in time of starting puberty was a confounding factor as BMD Z-score was adjusted for gender and age only.

This study was carried out in a single institution for disabled children in Hong Kong. Because of the need for sedation and exposure to radiation, guardians of children with more severe neurological disease tended not to consent for the study. Moreover, DXA could not be properly performed in patients with severe deformity. These children were not included in the study.

An inadequate number of patients in each group may have impacted the power of this study.

Nevertheless, the result showed a strong association for weight-for-age Z-score with TBLH BMD. We believe the association was highly statistically significant.

Children with CP are at risk of malnutrition that has a significant impact on linear growth, wound recovery, motor function, and even survival. In addition to poor linear growth, malnourished children with severe CP are likely to have poor bone mineralisation leading to painful pathological fracture. In a retrospective study of 107 CP children (90 non-ambulatory), weight-for-age Z-score proved to be the best predictor of BMD Z-score.[24] In the present study, we demonstrated a significant correlation of low weight-for-age Z-score with low BMD, with a relatively well-fitting model after adjusting for pubertal stage, calcium intake, and AED use. This is concordant with our previous findings in the same population in which there was a significant protective effect of increase in weight-for-age Z-score in reducing fracture risk (adjusted OR=0.41).[10] A recent review of 32 cross-sectional, cohort, case-control, and randomised controlled trials suggested that reduced bone density, impaired bone growth, and vitamin D deficiency may be seen in children treated with anticonvulsants.[25] In our study, individual vitamin D daily intake was calculated by dietitians. Sun exposure was limited in the institutional setting. Thus, we assumed that the calculated daily oral vitamin D intake correlated well with the serum vitamin D level. Although the daily vitamin D intake was similar in the low- and normal-BMD groups (P=0.297) as well as the study and control groups (P=0.702), 10 out of 32 subjects in the study consumed less than the recommended daily vitamin D intake (400 IU/day). To improve BMD and decrease fracture risk, regular nutritional assessment is necessary to identify malnourished children. Supplementation of vitamin D and calcium should be considered if the calculated daily need cannot be met. A nutritional rehabilitation programme should be implemented to optimise weight-for-age Z-score. Early gastrostomy tube placement should be considered in children with poor oral feeding. In children with weight-for-age Z score of ≤−2.0, serial BMD measurements can help to identify severe osteoporosis before fracture occurs. This window of time allows implementation of intensive nutritional rehabilitation, pharmacological intervention, and precautions in handling to prevent fracture occurrence.

Conclusion

Use of AED in non-ambulatory children with CP is unlikely to pose a detrimental impact on BMD. A low weight-for-age Z-score is a significant independent risk factor predictive of low BMD. Optimising nutritional status in this group of children is

paramount to improving bone mineralisation and thus decreasing pathological fracture.

Acknowledgement

Declaration

All authors have disclosed no conflicts of interest.

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