Official Journal of the European Paediatric Neurology Society

Original article

Determinants of low bone mineral density in children with epilepsy

Choong Yi Fong [a,*], Ann Nie Kong [a], Mazidah Noordin [a,b], Bee Koon Poh [c], Lai Choo Ong [a], Ching Ching Ng [d]

[a] Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[b] Paediatric Department, Universiti Institut Teknologi MARA, UiTM Medical Faculty, Sungai Buloh, Selangor, Malaysia
[c] Nutritional Sciences Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[d] Genetics and Molecular Biology, Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 23 December 2016
Received in revised form
15 June 2017
Accepted 15 October 2017

Keywords:
Epilepsy
Antiepileptic drug
Bone mineral density
Lifestyle
Genetic

ABSTRACT

Introduction: Children with epilepsy on long-term antiepileptic drugs (AEDs) are at risk of low bone mineral density (BMD). The aims of our study were to evaluate the prevalence and determinants of low BMD among Malaysian children with epilepsy.
Method: Cross-sectional study of ambulant children with epilepsy on long-term AEDs for >1 year seen in a tertiary hospital in Malaysia from 2014 to 2015. Detailed assessment of anthropometric measurements; environmental lifestyle risk factors; serum vitamin D, calcium and parathyroid hormone levels; genotyping of single nucleotide polymorphisms of genes in vitamin D and calcium metabolism; and lumbar spine BMD were obtained. Low BMD was defined as BMD Z-score ≤ -2.0 SD.
Results: Eighty-seven children with mean age of 11.9 years (56 males) participated in the study. The prevalence of low lumbar BMD was 21.8% (19 patients). Multivariate logistic regression analysis identified polytherapy >2 AEDs (OR: 7.86; 95% CI 1.03–59.96), small frame size with wrist breadth of <15th centile (OR 14.73; 95% CI 2.21–98.40), and body mass index Z-score < -2.0 (OR 8.73, 95% CI 1.17–65.19) as significant risk factors for low BMD.
Conclusion: One-fifth of Malaysian children with epilepsy on long-term AEDs had low BMD. Targeted BMD should be performed for those who are on >2 AEDs, underweight or with small frame size as they are at higher risk of having low BMD.

* *Corresponding author*. Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Fax: +60 3 79494704.
E-mail address: cyfong@ummc.edu.my (C.Y. Fong).
https://doi.org/10.1016/j.ejpn.2017.10.007

1. Introduction

The period of childhood and adolescence are critical stages of bone development. Peak bone mineral density (BMD) is accrued by 25 years of age and is an important determinant factor for the development of osteoporosis later in life.[1,2] Regulation of BMD is dependent on extrinsic (environmental lifestyle) and intrinsic (genetic) factors but the relative contribution of these factors in regulating BMD is not completely understood.[3,4] Environmental lifestyle factors such as calcium intake and physical activity have been shown to influence peak bone mass by modulating bone gain during childhood and adolescence.[5,6] Genetic factors like single nucleotide polymorphisms (SNPs) affecting enzymes important in vitamin D metabolism can also affect bone health.[7,8] These SNPs are potential life-long risk factors that can influence the individual's susceptibility to the osteopenic effects of antiepileptic drugs (AEDs) including BMD, independent of extrinsic environmental factors.

Long-term use of AEDs is a significant risk factor for impaired bone health including vitamin D deficiency and reduced BMD in children with epilepsy.[9–12] Reduced BMD in children with epilepsy is more pronounced in patients on enzyme-inducing AEDs, AED polytherapy, and in children with additional co-morbidities such as learning difficulties, cerebral palsy or if they are non-ambulant.[11,13] Studies have shown that reduced BMD was the most significant predictor of fracture risk, with fracture rates in patients on AEDs being 2–6 times higher than those in the general population with low BMD.[14–16] Early detection of low BMD in children on long-term AED is important to optimize bone health and potentially prevent premature fractures.

Dual-energy X-ray absorptiometry (DXA) is used to evaluate paediatric BMD with the lumbar spine being the recommended skeletal site for paediatric BMD measurement.[17] The International Society of Clinical Densitometry current recommendations for DXA scan in children include children with recurrent fractures, bone pain, bone deformities, osteopenia, and primary or secondary disorders that have been associated with increased fracture risk.[17] Impaired bone health in children on long-term AEDs is under-recognised and to date there are no recommendations on whether DXA scan should be performed on children on long-term AEDs.[17,18] At present, it is not routine practice to evaluate BMD in children on long-term AEDs in Malaysia.

The objective of this study was to evaluate the prevalence of low BMD in a cohort of ambulant Malaysian children with epilepsy on long-term AED. We also investigated the contribution of genetic and environmental lifestyle determinants of low BMD in this cohort.

2. Methods

2.1. Subject recruitment

This cross-sectional study was conducted in a paediatric neurology clinic at University Malaya Medical Centre (UMMC), Kuala Lumpur on ambulant children with epilepsy aged 4–18 years old. UMMC is a tertiary teaching hospital serving an urban population of 2 million and also acts as a referral centre for complex epilepsy cases. A total of 90 patients were enrolled in a 1-year period between April 2014 and April 2015. Three patients were excluded as they did not have the relevant bone health blood investigations; hence 87 patients were finally included in our study. The parents of this cohort of patients were approached with a verbal explanation of the study and also provided with a patient information sheet. Informed written consent was then obtained. Inclusion criteria included: children aged between 4 years old and 18 years old, on AEDs for more than 1 year, and able to ambulate independently. Exclusion criteria were intake of Vitamin D or calcium supplements for the last 6 months, or if there was co-existing hepatic, skeletal, renal or endocrine disorders. Children who had epilepsy with cerebral palsy who were able to independently walk (Gross motor function classification system level I–II) were also eligible for the study. This study was approved by the ethics committee of University Malaya Medical Centre (Ref: 1004.3) and the Malaysia Medical Research and Ethics Committee (Ref: NMRR-13-892-16933).

2.2. Clinical data collection

Clinical data of each patient were obtained using a standard proforma which included demographic data, past and current co-morbidities, anthropometric measurements, fracture history and skin pigmentation. Pubertal assessments were done based on Tanner staging with pubertal onset of boys defined as testicular volume >4 ml, and for girls defined as Tanner breast stage ≥2. Skin pigmentation was determined using the Fitzpatrick classification that consists of type 1 (lightest) to type 6 (darkest) skin pigmentation.[19]

Details of the child's epilepsy included seizure type, seizure frequency, epilepsy duration, AED regimen and AED duration. Enzyme inducing AEDs (EIAED) included carbamazepine, phenobarbitone, phenytoin, oxcarbazepine, and topiramate; and non-EIAEDs included sodium valproate, clobazam, lamotrigine, gabapentin, levetiracetam, zonisamide, and vigabatrin.

Anthropometric measurements included weight, height, body mass index (BMI) calculated as kg/m^2, waist circumference and wrist breadth. Weight was measured using calibrated TANITA digital scale Model 330 (TANITA, Japan) with accuracy to 0.1 kg, height was measured without shoes using SECA bodymeter Model 208 (SECA, Germany) with accuracy to 0.1 cm, waist circumference was measured with Lufkin tape model W606PM (Apex Tool Group, USA) with accuracy to 0.1 cm, and wrist breadth was measured with a bicondylar breadth calliper (Holtain, U.K.) with accuracy to 0.1 cm. Weight, height and BMI were classified based on World Health Organization (WHO) growth standards using height-for-age and BMI-for-age indicators.[20,21] BMI was defined as underweight if BMI-for-age Z-score was < −2.0, normal if Z-score was between −2.0 and + 1.0, and overweight or obese if Z-score was >+1.0. Waist circumference percentiles were derived from percentile curves from a previous Malaysian study.[22] Wrist breadth, a validated indicator of frame size, was obtained by measuring the distance