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Original Article

Prevalence of Vitamin D Deficiency and Insufficiency and Its Risk Factors in Paediatric Patients with Epilepsy on Anti-epileptic Drugs

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Abstract

Objective: The aim of our study is to evaluate the prevalence of vitamin D deficiency and insufficiency in children with epilepsy on anti-epileptic drugs (AED) in a regional hospital in Hong Kong. In addition, we would evaluate the possible risk factors of vitamin D deficiency and insufficiency in these patients. ***Method:*** A cross-sectional study was conducted in a regional hospital in April to May 2018 on paediatric patients who were on AED for at least one year. Review of medical records, anthropometric measurements, dietary and sunlight exposure behaviour assessments and blood tests (vitamin D assay and bone profile) were performed. Vitamin D deficiency is defined as serum 25-hydroxyvitamin D (25-OHD) level <30 nmol/L and insufficiency as 25-OHD level between 30-50 nmol/L. ***Results:*** Seventy-one children aged 3 to 18 years old were recruited into the study. The prevalence of vitamin D deficiency and insufficiency were 16.9% (12/71) and 52.1% (37/71) respectively. The two groups added up to a prevalence of 69.0% (49/71). In logistic regression analysis, the lack of holiday trip abroad within past three months (odds ratio 0.1, 95% confidence interval 0.02-0.73) was found to be a statistically significant independent risk factor for vitamin D deficiency and insufficiency. ***Conclusion:*** Vitamin D deficiency and insufficiency are highly prevalent in paediatric patients with epilepsy on AEDs in Hong Kong. However, it is similar to the prevalence found in healthy adolescents. This suggests that adolescents taking AEDs may not have an additional risk in lowering their vitamin D levels in this locality. We therefore would not advocate for routine screening for vitamin D level in adolescent epilepsy patients on AEDs in this locality, as it will not be cost-effective. Given that this is a cross sectional study, further interventional studies exploring the role of holiday trip abroad on vitamin D levels in paediatric epilepsy patients are warranted to substantiate a causality relationship.

Key words *Anti-epileptic drugs; Epilepsy; Paediatrics; Prevalence; Vitamin D deficiency*

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Introduction

Vitamin D deficiency is common in children worldwide, with a reported prevalence ranging from 15% to beyond 50%.[1-4] Prevalence varies among countries due to differences in risk factors and geographic reasons, including skin pigmentation, amount of sun exposure and dietary vitamin D intake.

Our body's sources of vitamin D are largely derived from dermal synthesis following ultraviolet B (UVB) solar radiation.[5] Very few foods contain vitamin D naturally. They include oil-rich fish, egg yolk and animal innards such as liver. Recommendation from the National Academy of Medicine for vitamin D intake in children between

1 and 18 years of age is 600 international units daily.[6] Hence, to ensure better nutritional intake, many food products in the market are fortified with vitamin D, such as cereal, milk products and fruit juices. The vitamin D absorbed is then converted by enzymes in the liver to 25-hydroxyvitamin D (25-OHD), the major circulating form, followed by conversion in the kidney to 1,25-OHD, the active form of vitamin D.

Screening for vitamin D status is most reliably determined by assay of serum 25-OHD. The precise definition of vitamin D deficiency or insufficiency is still a matter of debate. According to the Global Consensus Recommendations on Prevention of Nutritional Rickets,[7] vitamin D status can be classified into 3 categories:

1. Sufficient when 25-OHD level >50 nmol/L
2. Insufficient when 25-OHD level between 30-50 nmol/L
3. Deficient when 25-OHD level <30 nmol/L

Vitamin D deficiency carries significant health implications, especially in paediatric population. In infants and children, persistently low vitamin D levels may cause rickets,[5] which would result in soft and deformed bones, poor growth and bone fractures. In advanced vitamin D-deficient rickets, children could develop seizures or tetany, or may present as apnoeic spells, stridor, wheezing or hypotonia, due to severe hypocalcaemia. In addition, vitamin D deficiency reduces intestinal phosphorus absorption. Low serum phosphorus levels may cause muscle weakness and difficulties in standing or walking. Similarly, in adults, vitamin D deficiency may result in osteomalacia and osteoporosis, leading to higher chances of bone fractures. Treatment of vitamin D deficiency in children can optimise bone health and reduce rate of premature osteoporotic fractures later in adulthood.[5,8] Vitamin D deficiency is also associated with medical conditions, including obesity, inflammatory bowel disease, liver and kidney diseases.[6]

Several medications could affect vitamin D levels due to their effects on the metabolic pathway. Long term use of anti-epileptic drugs (AEDs) is found to be a risk factor for vitamin D deficiency and impaired bone health in children with epilepsy in previous studies.[9-11] It is postulated that hepatic cytochrome P450 (CYP) enzyme-inducing AEDs enhance hepatic metabolism of 25-OHD,[10] which would then be converted into inactive metabolites. Examples of enzyme-inducing AEDs include carbamazepine, phenytoin and topiramate. Non-enzyme-inducing AEDs can also affect bone health through direct effects on bone cells and inhibition of calcitonin secretion.[10,11] Examples of this group of AEDs include sodium valproate, levetiracetam, lamotrigine and clobazam.

In Malaysia, a study showed that up to 22.5% children with epilepsy taking AEDs had vitamin D deficiency and 19.7% had vitamin D insufficiency[12]. In Hong Kong, a study showed that 33.5% of infants at 3 months old had vitamin D deficiency (defined as serum 25-OHD concentration less than 50 nmol/L).[13] On the other hand, Cheung et al suggested that up to 64.7% and 11.4% of healthy adolescents aged 12 to 16 years were insufficient and deficient in vitamin D respectively (defined insufficiency as 25-OHD concentration 25-50 nmol/L and deficiency as 25-OHD less than 25 nmol/L).[14] However, there are so far no data on the prevalence of vitamin D deficiency and insufficiency in paediatric patients with epilepsy in this locality. There are also no clear guidelines on screening for vitamin D deficiency, or on the efficacy of prophylactic vitamin D supplementation.

The aim of this study is to evaluate the prevalence and potential risk factors for vitamin D deficiency and insufficiency in paediatric patients with epilepsy on AEDs, in a local hospital in Hong Kong.

Method

A prospective cross-sectional study was conducted in April and May 2018. Paediatric patients aged 3 to 18 years, who attended paediatric neurology clinic of Kwong Wah Hospital and have been on AEDs for at least 1 year were recruited. These patients were identified using the Clinical Data Analysis and Reporting System (CDARS) and International Classification of Diseases code (ICD-9). According to the study by Fong et al in 2016, prevalence of vitamin D deficiency in children with epilepsy on AEDs in Malaysia was 22.5%.[12] Taking the confidence interval at 95%, with the desired precision at 20% confidence interval width, the required sample size in this study would be at least 67 subjects. Ethical approval was obtained from the Kowloon Central Cluster Research Ethics Committee.

Exclusion criteria were defined as follows:

1. Current and prior intake of vitamin D or calcium supplement within past 6 months,
2. Ketogenic diet taken at present or over past 2 years,
3. Presence of hepatic, skeletal, renal or endocrine disorders,
4. Patient or legal guardian refusal to participate in this study.

Data Collection

Patients were interviewed by health care professionals at enrolment and medical records were reviewed. The following data were collected:

1. Demographic data including age, sex, ethnicity, maturity at birth, birth weight and socioeconomic class, which derived from the education level, occupation and income of the head of the household.[15]
2. Anthropometric measurements which include body weight, height and body mass index (BMI).
3. Epilepsy history and past medical history: AED regimen and duration of use, comorbid conditions including developmental delay, intellectual disability and concomitant drugs use. AEDs regime was then further classified into hepatic enzyme-inducing and non-enzyme-inducing groups.
4. Dietary assessment using a modified short food frequency questionnaire that recalls patient's intake over the past week.[16] Household measurement utensils were used to estimate portion sizes and analysis of dietary intake of vitamin D was performed.
5. Sun exposure behaviour – estimated from the time spent in outdoor activities per week and body parts that were exposed to the sun, which in turn derived a sun index as adapted from Barger-Lux and Heaney.[17] The sun index equates to hours of sun exposure per week multiplied by the fraction of body surface area (BSA) exposed to sunlight. Sun exposure behaviour was also estimated from whether patients had recent holiday trip abroad for at least 3 days, up to 3 months prior to the study.
6. Blood tests including vitamin D level and bone profile (calcium, phosphate and alkaline phosphatase (ALP)) were taken from patients. Vitamin D level was assessed by measuring serum 25OHD using the Waters TQD Liquid Chromatography-Tandem Mass Spectrometer System. For both 25OHD2 and 25OHD3, the limit of quantitation was 5 nmol/L with linear responses between 5 and 700 nmol/L. The coefficient of variation intra-and inter-assay were <6.7% and <8.8% respectively.

Statistical Analyses

Each subject's vitamin D level was classified as deficient, insufficient and sufficient according to the Global Consensus Recommendations on Prevention of Nutritional Rickets.[10] BMI (kg/m^2) was calculated and converted into BMI z-score by using the Cole's LMS method,[18] based on the normal references published for Hong Kong Chinese children.[19] Non-obese was defined as BMI z-score <=1.645 (<=95th percentile). The normality of data was assessed by Shapiro-Wilk test. As most of the distributions of the variables were non-normal, the descriptive statistics of these continuous variables were presented using the median and interquartile range (IQR). Differences in variables between groups were analysed using the Mann-Whitney U test or Student t-test. Categorical variables were analysed using the Chi-square test or Fisher exact test (used when more than 20% of cells have expected frequencies <5). To identify the risk factors associated with vitamin D deficiency and insufficiency, a multivariate logistic regression model was built using a stepwise selection procedure. The candidate variables included those with p-values <=0.1 in the univariate analysis. At each step of the model selection procedure, a variable was entered or removed from the model using the p-value cut-off 0.05. The odds ratio (OR) and the associated 95% confidence interval (CI) of each covariate in the final model was reported. To compare patients taking enzyme-inducing AEDs to patients taking non- enzyme-inducing AEDs, differences in variables were further analysed utilising the Kruskal-Wallis H test. A 2-tailed p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for -Windows, Version 22.0 (IBM Corp. in Armonk, NY, USA).

Results

One hundred and sixteen epilepsy patients on AEDs and followed up in our paediatric neurology clinic were identified using CDARS in our hospital. Within this group, 45 of them had to be excluded from the study as 31 of them were less than 3 years old or more than 18 years old during our study period. Ten patients were on AEDs for less than 1 year. Two patients were on vitamin D supplement and 2 patients did not consent to participate in the study as they refused to have blood tests. Hence, after exclusion, 71 participants were finally included in our study.

The demographic data, anthropometric measurements, sun exposure parameters and biochemical results are presented in Table 1. All our subjects were Asians. Their median age was 11.0 years old (IQR 8.0 to 16.0) and 59.0% (42/71) of them were male. Their median weight was 33.8 kg (IQR 25.4 to 47.8), BMI 17.0 kg/m^2 (IQR 15.6 to 19.4) and BMI z-score 0.151 (IQR -0.704 to 0.885).

Table 1 Comparisons of demographics and vitamin D sufficiency and insufficiency in children with epilepsy, n=71

	Overall (n=71)	**Sufficiency (>50 nmol/L) (n=22)**	**Insufficiency (<=50 nmol/L) (n=49)**	**P-value**
Preterm (<37 weeks)	13 (18.6%) (n=70)	1 (4.5%) (n=21)	12 (24.5%)	*0.090*
Male gender	42 (59.2%)	13 (59.1%)	29 (59.2%)	0.994
Age, year	11.0 (8.0 to 16.0)	10.5 (7.0 to 15.3)	12.0 (8.0 to 16.0)	0.176
Age >12 years old	34 (47.9%)	7 (31.8%)	27 (55.1%)	*0.069*
Birth weight, kg	3.1(2.6 to 3.4) (n=63)	3.2 (2.9 to 3.4) (n=19)	3.0 (2.6 to 3.3) (n=44)	0.231
Body weight, kg	33.8 (25.4 to 47.8)	31.4 (23.0 to 47.0)	36.6 (26.1 to 48.9)	0.305
Body height, cm	141.0 (129.5 to 157.5)	139.5 (126.1 to 154.1)	147.0 (131.5 to 159.0)	0.266
BMI, kg/m^2	17.0 (15.6 to 19.4)	16.7 (15.0 to 18.8)	17.2 (15.7 to 20.9)	0.486
BMI z score	0.151 (-0.704 to 0.885)	0.007 (-0.838 to 0.787)	0.371 (-0.618 to 0.942)	0.645
Socioeconomic class:				
Upper	1 (1.4%)	1 (4.8%)	0 (0%)	0.256
Middle	28 (39.4%)	7 (33.3%)	21 (42.9%)	
Lower	41 (57.7%) (n=70)	13 (61.9%) (n=21)	28 (57.1%)	
Development delay	43 (60.6%)	12 (54.5%)	31 (63.6%)	0.487
Intellectual disability	36 (50.7%)	8 (36.4%)	28 (57.1%)	0.105
Comorbid conditions	48 (68.6%) (n=70)	14 (63.6%)	34 (70.8%) (n=48)	0.547
Abnormal MRI brain finding	38 (58.5%) (n=65)	13 (65.0%) (n=20)	25 (55.6%) (n=45)	0.476
Abnormal ambulation	18 (25.4%)	5 (22.7%)	13 (26.5%)	0.733
History of fractures	4 (5.6%)	3 (13.6%)	1 (2.0%)	0.085
Abnormal bone profile	3 (4.2%)	1 (4.5%)	2 (4.1%)	1.000
Holiday trip abroad within three months	10 (14.1%)	8 (36.4%)	2 (4.1%)	*<0.001*
Use of sunscreen	10 (14.1%)	3 (13.6%)	7 (14.3%)	1.000
Sun exposure per week, hr	1.0 (0 to 6.0)	3.0 (0 to 7.3)	1.0 (0 to 6.0)	0.319
Fractions of BSA exposed to sunlight	0.45 (0.07 to 0.45)	0.45 (0.29 to 0.45)	0.31 (0.07 to 0.45)	*0.095*
Sun index	0.225 (0 to 1.89)	1.0 (0 to 3.8)	0.09 (0 to 1.8)	*0.100*
Dietary vitamin D intake per day (IU)	117.7 (22.1 to 224.5)	148.4 (19.0 to 263.9)	100.0 (23.8 to 195.3)	0.227
Other medications	9 (12.7%)	3 (13.6%)	6 (12.2%)	1.000
Serum vitamin D level (nmol/L)	43.0 (34.0 to 55.0)	61.0 (55.8 to 72.0)	39.0 (30.0 to 44.0)	*<0.001*
Duration of AEDs use (months)	41.0 (22.0 to 81.0)	37.0 (20.0 to 49.8)	46.0 (24.5 to 101.0)	0.189
Duration of AEDs use > 60 months	23 (32.4%)	4 (18.2%)	19 (38.8%)	*0.086*
Number of enzyme-inducing AEDs + non-inducing AEDs	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	0.783
Number of enzyme-inducing AEDs	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.844
Number of non-enzyme-inducing AEDs	1 (1 to 2)	1 (0 to 2)	1 (1 to 1.5)	0.877

Data are presented as median (interquartile range) or number (%)

BMI=body mass index, BSA=body surface area, Sun index=hours of sun exposure per week x fraction of BSA, AED=anti-epileptic drug

P-value highlighted in italics indicates p-value <=0.10

Forty-three of them had developmental delay (60.6%) and 36 of them (50.7%) had intellectual disability. Besides epilepsy, 48 subjects (68.6%) had other comorbid diseases. Nine subjects were also taking other medications on top of AEDs (12.7%), including baclofen, risperidone, folic acid and iron sulphate. Three had abnormal bone profile (4.2%) with mildly raised ALP level.

The prevalence of vitamin D deficiency and insufficiency were 16.9% (12/71) and 52.1% (37/71) respectively, adding up to a prevalence rate of 69.0% (49/71) in total. The median 25-OHD level was 43 nmol/L (IQR 10 to 96).

In univariate analysis, potential risk factors that were associated with vitamin D insufficiency include: preterm (<37 weeks), age >12 years old, fraction of BSA exposed to sunlight, sun index, lack of recent holiday trip abroad within 3 months, history of fractures and use of AED for more than 60 months (Table 1). Amongst these factors, multivariate logistic regression analysis identified that lack of recent holiday trip abroad within 3 months was independently associated with risk of vitamin D insufficiency, with odds ratio 0.1 (95% Cl 0.02 to 0.73) (Table 2).

Table 2 Multivariate logistic regression analysis of baseline predictors for vitamin D insufficiency (<=50 nmol/L)

Variable	Regression coefficient	OR (95% CI)	P-value
Preterm (<37 weeks)	1.379	4.0 (0.4 to 35.3)	0.216
Age >12 years old	0.559	1.7 (0.5 to 6.3)	0.393
History of fractures	-0.599	0.6 (0.03 to 8.70)	0.671
Holiday trip abroad within three months	-2.272	0.1 (0.02 to 0.73)	*0.023*
Fraction of BSA exposed to sunlight	0.497	1.6 (0.1 to 44.3)	0.768
Sun index	-0.194	0.8 (0.6 to 1.2)	0.337
Duration of AEDs use >60 months	1.007	2.7 (0.6 to 12.2)	0.186
Constant	0.593	1.8	0.370

BSA=body surface area, AED=anti-epileptic drug

P-value highlighted in italics indicates p-value <0.05

There was no statistically significant relationship between serum vitamin D level and dietary intake of vitamin D (Pearson correlation = 0.188; p=0.177) (Figure 1) or duration of AEDs use (Pearson correlation = -0.208; p=0.082) (Figure 2). In addition, the vitamin D levels did not show a significant difference between the group taking enzyme-inducing AEDs and the group taking non-enzyme-inducing AEDs. The differences in the subjects' baseline characteristics were essentially statistically insignificant as well (Table 3).

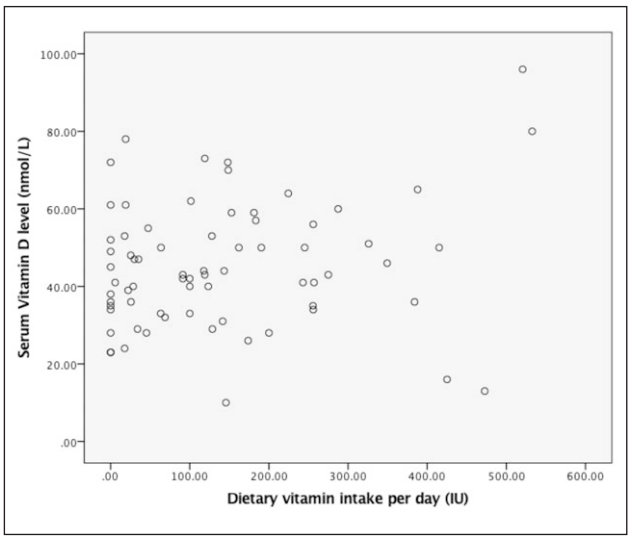

Figure 1 Correlation between serum vitamin D level and dietary intake of vitamin D.

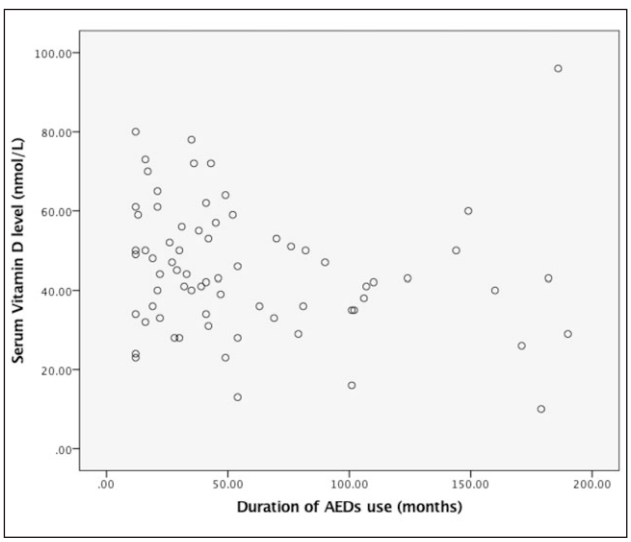

Figure 2 Correlation between serum vitamin D level and duration of AEDs use.

Discussion

To the best of our knowledge, our study is the first study investigating the prevalence of vitamin D insufficiency and deficiency in paediatric population with epilepsy in Hong Kong. When compared to a similar study carried out in Malaysia by Fong et al,[12] vitamin D deficiency and insufficiency are more prevalent in our subjects (69.0% vs 42.2%). Malaysia is located at the tropical region, with on average 6 hours of sunshine per day.[12] Hong Kong is located at the southern coast of China at latitude 22°N, surrounded by the South China Sea. It has a humid subtropical climate and has four seasons in a year. Overall, the mean sunshine duration per month is slightly less than

Table 3 Comparisons of demographics and vitamin D levels between enzyme inducing AEDs and non-enzyme-inducing AEDs groups

	Enzyme-inducing AEDs only (n=16)	Non-enzyme-inducing AEDs only (n=44)	Both (n=11)	P-value
Preterm (<37 weeks) (n=70)	3 (18.8%)	9 (20.9%) (n=43)	1 (9.1%)	0.666
Male gender	12 (75.0%)	23 (52.3%)	7 (63.6%)	0.270
Age, year	15.0 (11.5 to 16.8)	10.5 (7.3 to 14.0)	11.0 (6.0 to 17.0)	0.048
Age >12 years old	12 (75.0%)	18 (40.9%)	4 (36.4%)	0.046
Birth weight, kg (n=63)	3.2 (3.0 to 3.4) (n=13)	3.0 (2.5 to 3.3) (n=41)	3.3 (2.7 to 3.8) (n=9)	0.191
BMI z score	0.51 (-0.05 to 1.50)	-0.02 (-0.77 to 0.65)	0.54 (-0.53 to 1.12)	0.174
Socioeconomic class: (n=70)				
Upper	0 (0%)	1 (2.3%)	0 (0%)	0.277
Middle	10 (62.5%)	15 (34.9%)	3 (27.3%)	
Lower	6 (37.5%)	27 (62.8%) (n=43)	8 (72.7%)	
Development delay	7 (43.8%)	27 (61.4%)	9 (81.8%)	0.136
Intellectual disability	6 (37.5%)	22 (50.0%)	8 (72.7%)	0.196
Comorbid conditions (n=70)	10 (62.5%)	33 (75.0%)	5 (50.0%) (n=10)	0.257
Abnormal MRI brain finding (n=65)	7 (58.3%) (n=12)	23 (54.8%) (n=42)	8 (72.7%)	0.560
Abnormal ambulation	2 (12.5%)	13 (29.5%)	3 (27.3%)	0.401
History of fractures	2 (12.5%)	2 (4.5%)	0 (0%)	0.377
Abnormal bone profile	1 (6.3%)	1 (2.3%)	1 (9.1%)	0.543
Holiday trip abroad within three months	5 (31.3%)	5 (11.4%)	0 (0%)	0.051
Use of sunscreen	4 (25.0%)	4 (9.1%)	2 (18.2%)	0.268
Sun exposure per week, hr	3.5 (1.0 to 7.5)	0.5 (0 to 3.8)	2.0 (0 to 6.0)	0.132
Fraction of BSA exposed to sunlight	0.45 (0.33 to 0.45)	0.38 (0.07 to 0.45)	0.45 (0.07 to 0.45)	0.349
Sun index	1.35 (0.25 to 3.38)	0.08 (0 to 1.54)	0 (0 to 2.25)	0.076
Dietary vitamin D intake per day (IU)	123.5 (25.6 to 151.6)	100.7 (19.8 to 238.4)	100.0 (28.6 to 256.0)	0.806
Other medications	1 (6.3%)	6 (13.6%)	2 (18.2%)	0.627
Serum vitamin D level (nmol/L)	50.0 (33.3 to 59.8)	43.0 (36.0 to 54.5)	40.0 (26.0 to 47.0)	0.361
Duration of AEDs use (months)	35.0 (21.3 to 96.3)	43.0 (22.5 to 74.5)	41.0 (29.0 to 101.0)	0.861

Data are presented as median (interquartile range) or number (%)

BMI=body mass index, BSA= body surface area, Sun index=hours of sun exposure per week x fraction of BSA, AED=anti-epileptic drug

Malaysia, approximately 5 hours per day.[20]

Our study is a cross-sectional study, hence only association can be detected but causation cannot be confidently established. In our study, we were unable to demonstrate an association between our subjects' baseline sunlight exposure behaviour and their serum vitamin D levels. There are no local data looking into the optimal duration of sunlight exposure for vitamin D synthesis. Misra et al suggested that in people with light skin pigmentation, sufficient vitamin D synthesis is achieved by approximately 10 to 15 minutes of sun exposure per day between 10am and 3pm during spring to fall.[21] But for Asian Indians, due to different skin pigmentation, they may require three times as much sun exposure to achieve equivalent vitamin D concentrations.[22] Pearce and Cheetam suggested that 20 to 30 minutes of sunlight exposure on face and forearms at mid-day, two to three times per week, is sufficient to achieve healthy vitamin D levels in summer in the United Kingdom.[5] But for individuals with pigmented skin, exposure time or frequency need to be increased by two to ten-folds to get the same level of vitamin D synthesis as fair skinned young individuals.[5] From our data analysis, all our subjects were Asians, with mostly beige to light brown skin colour. Overall, they only had a median of 1 hour per week of sun exposure, which may not be adequate to achieve sufficient vitamin D synthesis. This could possibly explain why we were not able to identify a correlation with their serum vitamin D levels in our study. In addition, our study was conducted in spring, with humid weather and relatively less sunlight compared to the rest of the year. According to the information from Hong Kong Observatory, the monthly means of duration of sunshine were 101.7 and 140.4 hours in April and May,[20] but up to 212.0 hours in July. This may affect our subject's sunlight exposure behaviour and again the association with serum vitamin D levels. Furthermore, recall biases could be present when caretakers were enquired about their children's sun exposure behaviours.

On the other hand, we found that lacking holiday trip abroad in recent three months is an independent risk factor for vitamin D insufficiency. Ten subjects travelled abroad prior to our study. The countries that they visited included China, Thailand, Singapore and Malaysia. All the subjects and caretakers recalled having sunny weather during their travels. Their duration of stay ranged from 3 to 14 days (Table 4a and 4b). Thailand, Singapore and Malaysia are tropical countries in Southeast Asia, which have a relatively high solar UVB radiation throughout the year, and UVB is crucial for vitamin D dermal synthesis.[23] We did not fully explore the exact regions these subjects visited, or the amount of time they spent under the sun each day during their trips. We postulate that one may have longer time of outdoor activities during holiday trips, which would increase their chances of sunlight exposure and in turn vitamin D synthesis. More studies are needed to explore into this factor of holiday trip abroad and its association with a person's vitamin D levels. It is worth noting that our subjects travelled abroad up to 3 months prior to our study period. This may imply that after intense exposure to sunlight (during their trips in this study), one's vitamin D level could be maintained at a sufficient range for a certain period of time. Indeed, Kift et al found that adequate solar ultraviolent radiation exposure during the year could prevent 83% of healthy white-skinned adolescents from vitamin D deficiency during winter.[24] Nonetheless, being of different ethnic origin and skin pigmentation, further longitudinal studies are needed in this locality to investigate how long it lasts to maintain a person's adequate serum vitamin D level after a period of intense sunlight exposure, and whether it can become a protective factor for vitamin D deficiency and insufficiency.

Our study did not recruit healthy paediatric subjects as control and compare their vitamin D levels to our patients. Cheung et al looked at the prevalence of vitamin D insufficiency in healthy adolescents aged 12-16 years old in Hong Kong between 2009 and 2014.[13] They found out

Table 4a Countries visited by the 8 subjects in the vitamin D sufficient group three months prior to the study

Country	Duration of stay (days)	Travelling period
Thailand	3	February 2018
Thailand	6	April 2018
Thailand	5	March 2018
Singapore	5	April 2018
Singapore	5	February 2018
Malaysia	5	March 2018
China	14	February 2018
China	9	March 2018

Table 4b Countries visited by the 2 subjects in the vitamin D insufficient group three months prior to the study

Country	Duration of stay (days)	Travelling period
China	4	April 2018
China	10	February 2018

that 64.7% of the subjects were vitamin D insufficient (defined as 25-OHD level 25-50 nmol/L) and 11.4% were deficient (defined as 25-OHD level <25 nmol/L). When we classified our patients aged 12-16 years old using the definition of vitamin D levels Cheung et al adopted, we found that 63.6% of them were vitamin D insufficient and 13.6% deficient in our study. Comparing these figures from the two studies, there is no significant difference between the prevalence in healthy adolescents and in adolescents with epilepsy (Table 5). This suggests that adolescents taking AEDs may not have an additional significant risk in lowering their baseline vitamin D levels in this locality. On the other hand, Wang et al suggested that the prevalence of vitamin D deficiency was lower in children at preschool and primary school age than in adolescents in southeast China.[25] At the time of writing up this study, there are so far no data looking at the prevalence of vitamin D deficiency and insufficiency in healthy children at preschool and primary school age in Hong Kong. It will be interesting to explore whether the prevalence will be more significant in epilepsy patients than in healthy subjects when comparing younger paediatric age groups.

One of the limitations of our study is the relatively small sample size despite maximised efforts in recruiting subjects from our neurology clinic who fulfilled the inclusion criteria into our study. Only two subjects declined consent in participation due to the refusal of blood sampling. If we compared to Cheung et al study,[13] which recruited more than 500 healthy subjects, our small sample size of 71 subjects may considerably lower the chance of a significant result.

The association between use of liver enzyme-inducing AEDs and vitamin D levels was not demonstrated to be significant in this study. As mentioned, a small sample size could be a factor, but studies also suggested that non-enzyme inducing AEDs were associated with lower vitamin D levels and poor bone health.[10,26] Therefore, it may not be surprising a significant correlation was not identified here. Furthermore, the median number of AED our patients taking was only one, which made it difficult to evaluate the relationship between polypharmacy AEDs use and vitamin D level.

Whilst diet is considered a minor contributor to vitamin D status, from our data, we could see that all our subjects

Table 5 Comparisons of demographics and vitamin D level between paediatric patients with epilepsy and healthy adolescents (aged 12-16 years old) [Student t-test to compare their mean]

	Girls			Boys		
	Epilepsy children (n=9)	**Healthy children (n=333)**	**P-value**	**Epilepsy children (n=13)**	**Healthy children (n=230)**	**P-value**
Age, year	13.9 (1.7)	13.6 (1.1)	0.378	14.3 (1.6)	14.4 (1.1)	0.757
Body mass index, kg/m^2	18.3 (4.6)	19.6 (3.1)	0.222	18.7 (3.3)	19.8 (3.7)	0.296
Body height, cm	154 (7.1)	156 (6.4)	0.357	161 (14.5)	165 (8.9)	0.131
Body weight, kg	43.3 (12.3)	48.0 (9.3)	0.139	49.3 (14.8)	53.9 (12.7)	0.209
Serum vitamin D level (nmol/L)	37.0 (15.2)	40.1 (14.1)	0.516	47.3 (21.0)	40.4 (14.8)	0.112

Data are presented as mean (standard deviation)

Serum vitamin D level (nmol/L)	**Epilepsy children (n=22)**	**Healthy children (n=563)**	**P-value**
Sufficient (>50)	22.7% (5/22)	23.9% (135/563)	1.000
Insufficient (25-50)	63.6% (14/22)	64.7% (364/563)	1.000
Deficient (<25)	13.6% (3/22)	11.4% (64/563)	0.730
Deficient (<25)	13.6% (3/22)	11.4% (64/563)	0.730

Data are presented as number (%)

had inadequate dietary vitamin D intake, based on the recommended daily intake suggested by Ross et al.[6] This may explain the reason why we were not able to demonstrate a significant result on the correlation between dietary intake and vitamin D levels. Moreover, it may be of public health concern, in which education on sufficient dietary vitamin D intake should be reinforced to the whole paediatric population.

In our study, we did not perform dual-energy X-ray absorptiometry (DXA) scan on our patients to determine their bone mineral density (BMD) and correlate with serum vitamin D levels. Nevertheless, prior study has already demonstrated the association between low vitamin D level and low BMD in paediatric patients.[27]

To improve the study, larger sample size would certainly increase the precision of estimating the prevalence and delineating any additional potential risk factors for vitamin D deficiency. This could be achieved through collaboration among different paediatric centres in Hong Kong. In addition, repeating blood tests at different time points of the year could help to look at seasonal variation and assess any lasting effect of sunlight exposure during the year on subsequent vitamin D levels. Furthermore, measuring sunlight exposure accurately would also be an important area to increase precision. This can be done via wearing UV sensitive badges by subjects to collect reliable UVB exposure, which eliminates recall bias when enquiring caretakers for subjects' sunlight exposure behaviours.

Conclusion

Our study demonstrated that vitamin D insufficiency and deficiency are highly prevalent in paediatric patients with epilepsy on AEDs. However, the figures are comparable to that of the healthy adolescents in Hong Kong. Therefore, we would not advocate for routine screening for vitamin D levels in adolescent patients with epilepsy in this locality, which would not be cost-effective. Given the potential positive correlation between serum vitamin D levels and recent holiday trip abroad, further studies could be considered to investigate their relationship and implication.

Disclosure

None of the authors of this study has any conflict of interests to disclose.

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