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RESEARCH ARTICLE

25 - HYDROXY VITAMIN D LEVEL IN CHILDREN WITH EPILEPSY IN BASRA

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ABSTRACT

Background: The importance of vitamin D was recently emphasized when it was reported to be involved in cell differentiation, proliferation, immune function and important for optimal function of many organs and tissues throughout the body, including the central nervous system. This vitamin may reduce seizure frequency and treating adverse effect of anticonvulsant drugs so its supplementation is associated with decreased seizures as it regulates pro-convulsant and anticonvulsant factors.

Aim: A case-control study had been carried out to determine serum vitamin D level and other biochemical parameters in epileptic children and study it's relation to some selected variables who were treated with antiepileptic drugs for at least 6 months.

Methods: Thirty seven epileptic patients who had normal age - appropriate development; visited the out patients neurological clinic in Basra General Hospital, their ages ranged from 2-14 years from the1st of February to the end of July 2014. Forty four apparently healthy children and adolescent; were age and sex matched as a control group. Information regarding history of epilepsy; age of diagnosis, type and frequency of seizures over the past 3 months and type of antiepileptic drugs were recorded. All patients were under went physical examination including general and systemic examination. Growth parameters were assessed and body mass index (BMI) was calculated and applied to appropriate growth charts. A list of investigation was measured as; serum calcium, phosphorus, alkaline phosphatase and serum 25-Hydroxy vitamin D.

Results: Mean age of epileptic patients and control group was (7.67 ± 3.23) and (7.68 ± 3.5) year respectively. Two third of patients were younger than 10 years, as well as (86.5%) have normal body mass index, approximately 50% of patients received carbamazepine treatment for epilepsy and the duration of anti-epileptic drugs' therapy more than 24 months and more than 80% of patients were on monotherapy and were well controlled. The mean serum level of vitamin D was significantly low in epileptic patients than control group (21.41 ± 2.90), (67.59 ± 2.13) respectively as well as in children treated with polytherapy than those with monotherapy for epilepsy with higher level of alkaline phosphatase in epileptic patients than control group (299.09 ± 67.67) (122.21 ± 29.59) respectively (P value 0.000). On the other hand; levels of Calcium and phosphorus, serum level of blood urea and alanine aminotransferase (ALT) were not significantly differ among epileptic patient and control group (p value >0.05).

Conclusion: Children and adolescents treated with anti-epileptic drugs especially those patients on polytherapy therapy should given supplements of vitamin D to satisfy their bodies requirement.

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INTRODUCTION

Epilepsy describes a condition of susceptibility to recurrent seizures. (Friedman and Sharieff, 2006) It is considered to be present when 2 or more unprovoked seizures occur at an interval greater than 24 hr apart. The clinical diagnosis of epilepsy usually requires the occurrence of at least 1 unprovoked epileptic seizure with either a second seizure or enough EEG and clinical information to demonstrate predisposition to develop recurrences. (Mikati, 2011) Although, antiepileptic drugs (AED) remain the mainstay of treatment for epilepsy around the world. (Razazizan *et al*., 2013) It has shown that epileptic patients can exhibit a deficiency of vitamin D. (Baek *et al*., 2014) Twenty to 60% of AED users can develop rickets or osteomalasia due to induce hepatic oxidase activity throughout the microsomal enzymes cytochrome (P450), there promoting the catabolism of vitamin D and its derivatives. (Borba *et al*., 2004) The other mechanism of the AED involves a direct action on bone cells, increasing bone resorption and formation. In this way, the AED may influence bone turnover. Both mechanisms can be associated with a reduction in bone mineral density (BMD). (Pack *et al*., 2003) Vitamin D supplementation associated with decreased seizures. As it regulates proconvulsant and anticonvulsant factors. More specifically, this vitamin is involved in the down regulation of cytokine IL-6, which is a proconvulsant. (Bozzetto *et al*., 2012) Vitamin D has also been found to affect the expression of genes associated with Gamma-amino butyric acid (GABA); It is one of the main inhibitory neurotransmitters in the brain. (Féron *et al*., 2005) Also it has been shown to

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promote the expression of calcium binding proteins that are known to possess antiepileptic properties. (Evatt, 2012)

MATERIALS AND METHODS

A Case-control study has been carried out to determine serum level of vitamin D in 37 epileptic children and adolescent who were treated with antiepileptic drugs for at least 6 months. All the children had normal age - appropriate development; visited the out patients neurological clinic in Basra General Hospital from the 1st of February 2014 to the end of July 2014; their ages range from 2-14 years. Forty four healthy children and adolescent were aged and sex matched, selected from children visiting primary health care center for routine checkup or mild illnesses, have normal growth parameters were consider as control group.

Exclusion criteria

1. Calcium or vitamin D supplements for the last one month (Razazizan *et al*., 2013)
2. Neurological deficit as cerebral palsy or mental retardation
3. Chronic disease as history of chronic kidney disease, diabetes mellitus and bone deformities
4. Presence of conditions known to affect bone metabolism such as hepatic, hematological (e.g. sickle cell disease), rheumatologic, hyper-parathyroidism, hyperthyroidism, gastrointestinal disorders e.g., malabsorption as celiac disease. (Lee *et al*., 2007; Trunz *et al*., 2008)
5. Medications known to affect bone turnover e.g. steroid, bisphosphonate, thiazide and anticoagulant drugs. (Borba *et al*., 2004)

Data collection

A special questionnaire was designed for the purpose of the study including: Identity; name, date of birth, sex and residence. History of epilepsy; age of diagnosis, type and frequency of seizures over the past 3 months, well controlled is defined as seizures free for the last 3months. (Friedman and Sharieff, 2006) Type of antiepileptic drugs; doses and duration of antiepileptic drugs (AED), if monotherapy (single AED) or polytherapy (more than one AED) used. (Bozzetto *et al*., 2012) Informed consent had been taken from parents to be involved in the study. All patients were under went physical examination including general and systemic examination. Growth parameters were assessed, weight-for-height Z score, height-for-age Z score and weight-for-age Z score were estimated according to CDC/WHO normalized references. (Bikle, 2005) Body mass index (BMI) was calculated by weight in kilograms (kg) divided by the height in square meters $(m)^2$. (Wortsman *et al*., 2000) According to BMI percentiles growth charts underweight is < 50 %; normal weight 50 - 85 % and over weight is > 85 %. (Razazizan *et al*., 2013)

Laboratory procedures

A list of investigations was measured by spectrophotometer (Cobas C 111), Serum calcium (Ca^+), serum phosphorus (Ph), serum Alkaline phosphates (ALPh), blood urea and alanine aminotransferase (ALT). Serum 25-Hydroxy vitamin D (25OH); was measured by ELISA test. Very severe vitamin D deficiency is <5 ng/ml; deficiency level <15 ng/ml; insufficiency level (15-20 ng/ml); and consider as sufficient if its level 20-30 ng/ml. Optimal level is 30-50 ng/ml and the upper normal located between 50-70 ng/ml. (Hollick, 2007)

Statistical analysis

Data were analyzed using SPSS software version 18. Data were expressed by mean ± Standard Deviation (SD) and Standard Error (SE) Comparison was performed by using Chi-Square test. The t-test was used for quantitative comparison and between two mean of different samples. Comparisons between groups were made by using the one way analysis of variance (ANOVA) test .Logistic regression analysis was done for the analysis of different marker, by using Odd Ratio (OR) and 95% Confidence Interval (CI). For all tests p-value of <0.05 was considered as statistically significant.

RESULTS

Selected demographic characteristics of epileptic patients and control

A total of 37 epileptic patients and 44 children and adolescent as control group were included in the study, their ages ranged from 2-14 years and mean age was (7.67± 3.23); (7.68 ± 3.50) years respectively. Twenty eight (75.7%) of epileptic children were younger than 10 years, As well as (86.5 %) had normal weight; their BMI was 50-85%. Table 1 shows that (51.4%) of patients received carbamazepine treatment for epilepsy. As well as more than 80% patients were well controlled on monotherapy and 54.1% of patients were on AED therapy for more than 24 months.

Biochemical Parameters among epileptic Patients and control group

It has been found that vitamin D level was significantly lower among epileptic patient compared to healthy control group (p value <0.05), as well as alkaline phosphatase significantly higher among epileptic patients. P value <0.000 (Table 2)

Vitamin D level and selected variable in epileptic patients

Table 3 shows that; (13.5% and 24.3%) of epileptic patients had (severe deficiency level < 5ng/dl and deficient level< 15ng/dl) respectively with higher frequency in patients with generalized seizure (77.8%), receiving poly therapy (55.6%); with duration of anti-epileptic drugs >24 months (66.7%). On the other hand (39.7%) of epileptic patients had sufficient level (20-30ng/dl) mainly those with partial seizure (81.8%); treated with carbamazepine (72.7%) and receiving mono therapy (100%)

Mean vitamin D in relation to selected characteristics of epileptic children

Epileptic children receiving poly therapy AED had significantly lower level of vitamin D than those children treated with mono therapy (9.30 ± 2.63), (24.2 ± 3.32) respectively. As well as poorly controlled epileptic children who continue on AED for more than 24 months had significantly low vitamin D level (p-value <0.05). By using one way Anova test between vitamin D level and selected variables shows that significant differences between the type of therapy and vitamin D when level <15 ng/ml (p-value 0.03). As well as; there is significant differences between poor controlled

Table 1. Selected characteristics of epileptic patients

Variable		No.	%
Age (years)	2-5	12	32.4
	>5-10	16	43.3
	>10-14	9	24.3
Sex	Male	21	56.8
	Female	16	43.2
BMI	<50%	4	10.8
	50 - 85%	32	86.5
	>85%	1	2.7
Type of seizure	Partial	20	54.1
	Generalize	17	45.9
Seizure control	Well control	32	86.5
	Poor control	5	13.5
	Carbamazepine (CBZ)	19	51.4
Type of AED	Valproic acid (VPA)	11	29.7
	CBZ + VPA	3	8.1
	VPA +Clonazepam(CZP)	3	8.1
	CBZ + VPA + CZP	1	2.7
Type of therapy	Monotherapy	30	81.1
	Polytherapy	7	18.9
Duration of	6-12	12	32.4
AED therapy	>12-24	5	13.5
(months)	> 24	20	54.1
Total		37	100%

Table 2. Biochemical Parameters

Variables	Mean ± SD		P-value
	Epileptic patients	Control group	
Vitamin D (ng/ mL)	21.41 ± 2.90	67.59 ± 2.13	0.000
Calcium (mg/dL)	8.09 ± 0.97	8.81 ± 1.63	0.620
Phosphorus (mg/dL)	0.81 ± 0.42	1.48 ± 0.36	0.812
Alkaline phosphatase (IU/L)	299.09 ± 67.67	122.21 ± 29.59	0.000
ALT (IU/L)	11.09 ± 1.13	10.89 ± 1.58	0.427

Table 3. Vitamin D level in relation to selected variables of epileptic patients

Variables		Severe deficiency≤ 5		Deficiency < 15		Insufficiency 15-20		Sufficiency 20-30		Optimal >30	
		No	%	No	%	No	%	No	%	No	%
Age (years)	2-5	1	20	4	44.4	2	28.6	2	18.2	0	0
	>5-10	2	40	4	44.4	1	14.3	7	63.6	3	60
	>10-14	2	40	1	11.1	4	57.1	2	18.2	2	40
Sex	Male	1	20	6	66.7	5	71.4	6	54.5	3	60
	Female	4	80	3	33.3	2	28.6	5	45.5	2	40
BMI	<50%	1	20	1	11.1	0	0	2	18.2	0	0
	50-85%	4	80	8	88.9	7	100	8	72.7	4	80
	>85%	0	0	0	0	0	0	1	9.1	1	20
Type of seizure	Partial	3	60	2	22.2	4	57.1	9	81.8	3	60
	Generalize	2	40	7	77.8	3	42.9	2	18.2	2	40
AED	CBZ	3	60	2	22.2	3	42.9	8	72.7	3	60
	VPA	1	20	2	22.2	3	42.9	3	27.3	2	40
	CBZ+VPA	1	20	2	22.2	0	0	0	0	0	0
	VPA+CZP	0	0	2	22.2	1	14.3	0	0	0	0
	VPA+CBZ+CZP	0	0	1	11.1	0	0	0	0	0	0
Type of therapy	Mono	4	80	4	44.4	6	85.7	11	100	5	100
	Poly	1	20	5	55.6	1	14.3	0	0	0	0
Duration of AED (months)	<24	0	0	3	33.3	0	0	5	45.5	2	40
	>24	5	100	6	66.7	7	100	6	54.5	3	60
Total		5	13.5	9	24.3	7	18.9	11	39.7	5	13.5

Table 4. Mean vitamin D level in relation to selected characteristic of epileptic patients

Variable		Mean Vitamin D level ± (SE)	P- value
Age(years)	2-5	20.86 ± 5.21	0.921*
	>5-10	22.60 ± 3.90	
	>10-14	20.02 ± 3.65	
Sex	Male	22.02 ± 3.77	0.980
	Female	20.61 ± 4.69	
BMI	<50%	2o.15 ± 8.20	0.060*
	50-85%	20.42 ± 3.12	
	>85%	58.10 ± 0.00	
Type of seizure	Partial	25.71 ± 4.32	0.073
	Generalize	16.36 ± 3.81	
Types AED	CBZ	25.64 ± 4.42	0.062*
	VPA	21.89 ± 3.54	
	Other medication	9.30 ± 6.85	
Type of therapy	Monotherapy	24.24 ± 3.23	0.023
	Polytherapy	9.30 ± 2.63	
Seizure control	Well	23.11 ± 3.17	0.001
	Poor	10.56 ± 3.58	
Duration of AED (months)	<24	30.50 ± 3.78	0.032
	≥ 24	18.04 ± 3.11	

*Anova used to measure p-value for age, BMI and type of antiepileptic drugs
T-test was used measure p-value for all variables.

Table 5. Risk factor for low serum level of vitamin D

Variable	p-value	Odd ratio	95% confidence interval	
			Lower value	Upper value
Age	0.136	1.547	0.068	13.720
BMI	0.831	1.352	0.075	11.463
Type of AED	0.060	1.178	0.028	11.23
Type of therapy	0.020	6.991	0.062	0.258
Seizure control	0.128	1.497	0.075	13.621
Duration of AED	0.928	1.341	0.048	11.142

seizure and vitamin D level <15 ng /ml (p-value 0.02) and significant differences also found between epileptic children who taken AED more than 24 months and vitamin D level < 15ng/ml. (Table 4)

Logistic regression analysis of selected variable with low level of vitamin D in epileptic patients

Table 5 shows that patients on poly therapy is significantly have low level of vitamin D (p-value <0.05), Odd ratio (6.991). But there is no statistically significant correlation of other variable (age, BMI, type of AED, seizure control and duration of therapy) with low level of vitamin D in Epileptic children.

DISCUSSION

In this study the mean level of vitamin D is low among epileptic patients compared with healthy children. Similar result was concluded by Alison *et al* in New Yourk and Silvana *et al* in Brazil. (Alison, 2003; Silvana *et al*., 2000) The mean level of calcium for epileptic patients was in the normal limit this is in agreement to that reported by Razazizan *et al* in Iran, (Razazizan *et al*., 2013) which could be due to secondary hyperparathyroidism to maintain normocalcimia. (Misra, 2010) and in contrast to Babyigit *et al* in Turkey (Babayigit *et al*., 2006) whom concluded that epileptic children have low level of calcium than control; possibly due to direct impact of AED on bone mineral density and intestinal transport and the effect of hypovitaminosis D which lead to decreased absorption of the calcium in intestine. (Babayigit *et al*., 2006; Okesina *et al*., 1991) Alkaline phosphatase is an important biochemical marker of bone metabolism in epileptic patients. (Razazizan *et al*., 2013) In this study, the mean level of alkaline phosphatase is significantly higher in epileptic children than control group, this result is similar to that reported by Razazizan *et al* in Iran, Babyigit *et al* in Turkey and Okesina in Nigeria. (Razazizan *et al*., 2013; Babayigit *et al*., 2006; Okesina *et al*., 1991) Because AED are inducers of the hepatic cytochrome P_{450} system which promote the metabolism of 25-hydroxyvitamin D (25-OHD) to less biologically active analogues, resulting in decreased bone mineralization, decreased intestinal calcium absorption, increased calcium mobilization from the skeleton to maintain eucalcemia, and decreased bone density. (Babayigit *et al*., 2006) Also this study revealed that more than one third of patients had sub optimal vitamin D level while less frequent of patients who have optimal vitamin D level, this result is in agreement with Menton *et al* in India. (Menon, 2010) There is higher frequency of vitamin D deficiency among young children with epilepsy in Basra than older children, this is in agreement with Baek *et al* in Korea. (Baek *et al*., 2014) Which could be related to age- biological processes or less physical activities with increasing age which lead decrease sunlight exposure. BMI of epileptic patients in Basra are not significantly associated with decrease level of vitamin D, This is in agreement with Misra *et al* in India. (Alison, 2003) But in contrast to a study carried out by Baek *et al* in Korea and Lagunova *et al* in Norway (Baek *et al*., 2014; Lagunova *et al*., 2009) whom show; that the level of vitamin D decrease with increasing BMI which can be explained by the fact that peoples with high BMI usually have a high content of body fat, acting as a reservoir for lipid-soluble vitamin D. Current study reveals that no significant association between type of AED (CBZ, VPA or other AED) and vitamin D level . This is in agreement with a study conducted by Menon *et al* in India. (Menon, 2010) Which shows that the level of vitamin D decrease irrespective to the type of AED used. This is in contrast to Valsamis *et al* in USA and Kim *et al* in Korea. (Valsamis *et al*., 2006; Kim *et al*., 2007) They found that bone turnover is higher with hepatic enzyme inducing AED such as (CBZ) than non–inducing AED as (VPA). (Valsamis *et al*., 2006) That can be explained by enzyme inducing AED (PHT, PB, CBZ) and enzyme inhibiting AED (VPA) affected the 25(OH)D metabolism at sub-therapeutic doses of AED. Patients on polytherapy demonstrated significantly lower 25(OH) D levels than patients on monotherapy, This result is in agreement with a study by Sina *et al* in Germany. (Kim *et al*., 2007) And Menon *et al* in India. (Okesina *et al*., 1991) It can be explained by effected of AED on vitamin D which more increase by using more than one AED (polytherapy). (Okesina *et al*., 1991) In contrast to a study done by Beak *et al* in Korea. (Baek *et al*., 2014) Who found no significant difference in level of vitamin D among patient in monotherapy and polytherapy. In Basra the effect of un controlled seizure had been found to be associated with low vitamin D level. This is similar to the result concluded by Behar *et al* in Hungary. (Behav, 2012) Possible explanation that normal level of vitamin D in serum has anticonvulsive role, As well as any poorly controlled patient already kept on many AED to control seizures. (Behav, 2012) Duration of AED therapy is significantly correlated with vitamin D level, lower level of vitamin D for epileptic children who received AED for more than 24 months than those who received AED for less than 24 months. Similar result was reported by Misra *et al* in India, Back *et al* in Korea and Menon *et al* in India. (Baek *et al*., 2014; Misra, 2010; Menon, 2010) Whom concluded that there is significant impaction of AED on level of vitamin D and this effect increase with longer duration of therapy and low dietary intake of vitamin D. (Menon, 2010) In contrast with a study of Yuan Guo in Canada (Guo *et al*., 2001) and Razazizen *et al* in Iran (Razazizan *et al*., 2013) whom found; no relation between vitamin D level and duration of AED, that can be possibly explained by using a single drug and children recruited in the study have adequate nutritious diet. (Razazizan *et al*., 2013)

Recommendation

Vitamin D_3 supplement should be given for all epileptic children even before initiation of anti-epileptic therapy and children with epilepsy should follow well balanced diet and

good nutritional habits and healthy lifestyle to optimize seizure control.

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