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Effect of antiepileptic drugs on Vitamin D status in children with idiopathic epilepsy

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Abstract: Background: Epilepsy is a common neurological disorder that affects individuals of all ages. Epileptic children experience fractures 2-6 times more frequently than the general population. Treatment with anti epileptic drugs (AEDs) is chronic and associated with significant metabolic effects including decreased bone mass and increased bone fractures. In pediatric patients, controversies still remain regarding the effect of anticonvulsants on vitamin D levels and bone health. **Objectives:** This study is to evaluate the effects of the antiepileptic drugs (AEDs): Valproate, Carbamazepine, Levetiracetam and Topiramate on the biochemical markers of bone metabolism (Vitamin D, Parathormone, Alkaline phosphatase, serum calcium and phosphorus) in children with idiopathic epilepsy. **Methods:** Comparing clinical and lab results regarding demographic data, levels of (serum calcium, serum phosphorus, alkaline phosphatase, parathyroid hormone and 25-OH Vitamin D) in 100 children with idiopathic epilepsy aged 6-15 years and 50 healthy children of the same age and sex. **Results:** There was significant decrease in serum calcium and phosphorus levels in children treated with Valproate ($p1<0.001$) and carbamazepine ($p2<0.001$) and the control. There was significant increase in serum alkaline phosphatase and parathormone levels in both valproate treated group ($p1<0.001$) and carbamazepine treated group ($p2<0.001$) and the control. There was significant decrease in the mean serum 25-OH Vitamin D level in both valproate treated group ($p1<0.001$) and carbamazepine treated group ($p2<0.001$) and the control. There was inverse correlation between the duration of treatment with valproic acid and carbamazepine and the mean level of 25-OH Vitamin D. **Conclusion:** Vitamin D deficiency is common in children with epilepsy who had received valproate or carbamazepine as a monotherapy for twelve months. There was inverse correlation between serum 25-OH Vitamin D level and duration of treatment with valproate and carbamazepine. Levetiracetam and Topiramate have no significant effect on 25-OH vitamin D level on the studied children.

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Key words: Epilepsy - antiepileptic drugs – bone density – vitamin D

1. Introduction

Epilepsy is one of the most common neurological disorders in the pediatric age group. By the neurobiologic, cognitive, psychologic and social consequences of epilepsy, it is considered to be a serious neurologic disorder that often requires lifelong treatment. (1) Anti epileptic drugs are frequent and selection of antiepileptic drug is a challenging task. Age, sex, type of seizures and presence of other medical conditions should be considered during choice of antiepileptic drug. AEDs include a variety of drugs that may lead to catabolism of vitamin D and hypocalcemia. (2) Vitamin D deficiency and its effects on bone health in children with epilepsy is becoming an increasingly recognized health care concern. In addition, vitamin D deficiency may lead to other significant health problems, such as cancer, multiple sclerosis, asthma and type 1 diabetes. (3)

Aim of the Work

This study is carried out to evaluate the effects of the antiepileptic drugs (AEDs): Valproicacid, Carbamazepine, Levetiracetam and Topiramate on the biochemical markers of bone metabolism which are (Vitamin D, Parathormone, Alkaline phosphatase, serum calcium and phosphorus) in children with idiopathic epilepsy.

2, Patients and Methods:

This study was carried out in Tanta University Hospital, Pediatric Department, Neurology Unit. This study was done after informed consent from the parents. In this study, one hundred (100) children with idiopathic epilepsy on chronic use of AEDs: carbamazepine, valproic acid, levetiracetam and topiramate for at least one year of treatment were selected from those attending the pediatric neurology out-patient clinic and were enrolled in the study with the age range from 6-15 years. These patients were

grouped according to their antiepileptic drug treatment into four groups:

Group 1: 30 patients received valproic acid as monotherapy.

Group 2: 30 patients received carbamazepine as monotherapy.

Group 3: 20 patients received levetiracetam as monotherapy.

Group 4: 20 patients received vtopiramate as monotherapy.

Fifty neurologically healthy children with the same age and sex were served as the control group.

Study Duration: The study was carried out in duration of 1 year from November 2017 to November 2018.

Inclusion criteria:

1-Children with idiopathic epilepsy aged from 6-15 years.

2-Children with normal Magnetic Resonant Imaging (MRI) brain.

3-Children with well controlled epilepsy.

4- Normal intelligence.

Exclusion criteria:

1- Children with metabolic bone diseases.

2- Children with renal, hepatic, endocrinal diseases.

3- Children with epilepsy who are seizure free and off medications.

4- Children with vitamin D or calcium supplementation.

5- Children with symptomatic epilepsy or structural brain lesions.

All patients were subjected to the following:

1. Complete history taking: This included personal, family, perinatal, developmental, medical, vaccination history. Full history about the initial presentation and frequency of seizures, age of onset, drug intake before, history of previous fractures and family history of metabolic bone disorders.

2. Thorough physical examination: This included general examination including weight and height and local chest, cardiac, abdominal and neurological examination.

3. Routine neuro-imaging & electro-physiological study for children with idiopathic epilepsy: a) Magnetic resonance imaging (MRI) was done for children with epilepsy for exclusion of underlying structural cause such as tumors, abscess, old stroke or mesial temporal sclerosis.

b) Electroencephalogram (EEG) was done for children with epilepsy for assurance whether the seizure is epileptic or other paroxysmal event, focal or generalized, and if it belongs to specific syndrome.

4. The diagnosis of epilepsy was done according to the standards of the International League Against Epilepsy (ILAE) 2017. (4)

5. Laboratory study: Blood samples were obtained to determine biochemical parameters of bone metabolism including serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D.

Statistical Methods

The analysis was calculated by SPSS V.21, Year (2016). Furthermore, the qualitative parameters were described by number of frequency and percentage while the quantitative variables were described by mean, median, standard deviation and range. In addition, ANOVA test was used for comparison among different times in the same group in quantitative data. While the comparison of qualitative variables between the two groups were calculated by Chi Square test.

3. Results:

Patient demographics:

100 children with age ranging from 6-15 years were divided into 4 groups according to their type of anti-epileptic drugs and compared with 50 children of the same age and sex who were served as the control group. (Table 1)

- Valproic acid treated group: age range from 6-14 years, 17 male and 13 female, all of them have generalized seizures.
- Carbamazepine treated group: age from 6-13 years, 19 male and 11 female, 28 of them have partial seizures.
- Levetiracetam treated group: age range from 6-10 years, 3 male and 17 female, 10 of them have generalized seizures.
- Topiramate treated group: age range from 6-15 years, 12 male and 8 female, 17 of them have generalized seizures.

Serum Calcium level (mg/dL) among the studied group:-

Table (2) and shows comparison between the serum calcium level in children on antiepileptic drugs and the control group.

Mean Serum calcium level in Valporate treated group was (8.06+0.33), in carbamazepine treated group (7.56+0.46), in Levetiracetam treated group (9.26+0.26), in Topiramate treated group (9.27 +0.35) and in the control (10.03+0.50).

There was significant decrease in serum calcium level in children treated with Valproic acid ($p1<0.001$) and carbamazepine ($p2<0.001$) when compared with the control group, while there was no significant difference in serum calcium level between the children treated with Levetiracetam ($p3=0.56$) and Topiramate ($p4=1.01$) and the control group.

Table (1): Demographic data of the studied groups:

	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	Levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Age (years)					
Range	6 – 14	6 - 13	6 – 10	6 – 15	6 - 15
Mean ± SD	7.33 + 0.31	7.86 + 1.62	7.80 + 1.04	8.87+ 2.07	8.08 + 1.57
Median	7	7.75	7.75	8.75	8.00
Sex					
Male	17 (56.7%)	19 (63.3%)	3 (15%)	12 (60%)	27 (54%)
Female	13 (43.3%)	11 (36.7%)	17 (85%)	8 (40%)	23 (46%)
Duration of treatment (month)					
Range	12 – 40	12 - 36	12 – 30	12 – 36	
Mean ± SD	22.03 + 7.08	20.06 + 7.06	17.70 + 4.96	19.45 + 5.86	
Median	23	21	17.0	20	
Type of convulsion					
Generalized	30 (100%)	2 (6.7%)	10 (50%)	17 (85%)	
Partial	0 (0.0 %)	28 (93.3%)	10 (50%)	3(15%)	

Table (2) Serum calcium level (mg/dl) among the studied groups

Serum Calcium (mg/dl)	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Range	7.43 – 8.50	7.23- 8.90	8.80 – 9.74	8.08 – 9.98	9.31– 10.94
Mean ± SD	8.06 + 0.33	7.56 + 0.46	9.26 + 0.26	9.27 + 0.35	10.03 + 0.5
Median	8.11	8.70	9.26	9.20	10.08
F	99.45				
P	0.001*				
Sig. bet. Groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.56$, $p_4=1.01$				

F, p: F and p values for **ANOVA test**, Sig. bet. groups was done using **Post Hoc Test (LSD)**
P1: Valproic treated Group vs Controls.
P2: Carbamazepine treated Group vs Controls.
P3: levetiracetam treated Group vs Controls.
P 4: topiramate treated Group vs Controls.
*: Statistically significant at $p \leq 0.05$

Table (3) Serum phosphorus level (mg/dl) in the studied groups

Serum Phosphorous	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Range	2.95 – 4.5	4.20 - 5.00	4.33 – 6.45	4.32 – 6.32	4.34 - 6.5
Mean ± SD	4.03 + 0.41	4.57 + 0.25	5.45 +0.68	5.48 +0.66	5.35 + 0.63
Median	4.20	4.80	5.51	5.60	5.31
F	47.46				
P	0.001 *				
Sig. bet. Groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.95$, $p_4=0.90$				

F, p: F and p values for **ANOVA test**, Sig. bet. groups was done using **Post Hoc Test (LSD)**
P1: Valproic treated Group vs Controls.
P2: Carbamazepine treated Group vs Controls.
P3: Levetiracetam treated Group vs Controls.
P 4: Topiramate treated Group vs Controls.
*: Statistically significant at $p \leq 0.05$

Serum Phosphorus level (mg/dL) among the studied groups:-

Table (3) shows comparison between serum phosphorus level in children on antiepileptic drugs and the control group.

Mean Serum phosphorus level in Valproic acid treated group (4.03+0.41), in Carbamazepine treated group (4.57+0.25), in Levetiracetam treated group (5.45+0.68), in Topiramate treated group (5.48+0.66) and in the control (5.35+0.63).

There was significant decrease in serum phosphorus level in children treated with Valproic acid ($p1<0.001$) and carbamazepine ($p2<0.001$) while there was no significant difference between Serum phosphorus level in Levetiracetam treated group ($p3=0.95$) and Topiramate ($p4=0.90$) and the control group.

Serum Alkaline phosphatase level (unit/L) among the studied group:-

Table (4) shows comparison between serum alkaline phosphatase level (unit/L) between children on antiepileptic drugs and the control group.

Mean Serum alkaline phosphatase in valproic acid treated group (452.8+36.1), in carbamazepine treated group (476.6+37.5), in Levetiracetam treated group (174.5+49.6), in topiramate treated group (169.2+55.2) and in the control (180.4+54.1)

There was significant increase in serum alkaline phosphatase level in both valproic acid treated group ($p1<0.001$) and carbamazepine treated group ($p2<0.001$) in comparison with the control while there was no significant difference in alkaline phosphatase level in Levetiracetam treated group ($p3=0.99$) and in Topiramate treated group ($p4=0.89$) and the control.

Table (4): Serum Alkaline Phosphatase (Unit/L) level among the studied groups

Serum Alkaline Phosphatase (Unit/L)	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Range	395 - 515	400 – 545	107 – 277	107 – 283	90 – 294
Mean ± SD	452.8 + 36.1	476.6 + 37.5	174.5 + 49.6	169.2 + 55.2	180.4+ 54.1
Median	458.5	477.5	162	158.5	171.50
F	395.5				
P	0.001 *				
Sig. bet. Groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.99$, $p_4=0.89$				

F, p: F and p values for **ANOVA test**, Sig. bet. groups was done using **Post Hoc Test (LSD)**
P1: Valproic treated Group vs Controls.
P2: Carbamazepine treated Group vs Controls.
P3: Levetiracetam treated Group vs Controls.
P 4: Topiramate treated Group vs Controls.
*: Statistically significant at $p \leq 0.05$

Table (5): Serum parathyroid hormone (pg/ml) level among the studied groups

Serum parathyroid hormone (pg/ml)	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Range	33 – 66.4	25.4 – 70	24.8 – 50.5	20.6 – 54	21.5 – 55.2
Mean ± SD	41.76 + 9.16	44.62 + 10.76	36.52 + 7.60	37.74 + 9.92	33.66 + 8.31
Median	41.05	42.6	36.9	35.9	32.99
F	3.71				
P	0.014 *				
Sig. bet. Groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.76$, $p_4=0.45$				

F, p: F and p values for **ANOVA test**, Sig. bet. groups was done using **Post Hoc Test (LSD)**
P1: Valproic treated Group vs Controls.
P2: Carbamazepine treated Group vs Controls.
P3: Levetiracetam treated Group vs Controls.
P 4: Topiramate treated Group vs Controls.
*: Statistically significant at $p \leq 0.05$

Serum Parathyroid hormone level (pg/ml) among the studied group:-

Table (5) shows comparison between serum parathyroid hormone level between children on antiepileptic drugs and the control group.

Mean parathyroid hormone level in valproic acid treated group was (41.76+9.16), in carbamazepine treated group was (44.62+10.76), in Levetiracetam treated group (36.52+7.60), in topiramate treated group was (37.74+9.92) and in the control group was (33.66+8.31).

There was significant increase in mean parathyroid hormone level in valproic acid treated group ($p1<0.001$) and in carbamazepine treated group ($p2<0.001$) when compared with the control while there was no significant difference in mean serum

parathyroid hormone level in levetiracetam treaded group (p3=0.76) and in topiramate treated group (p4=0.45) and the control group.

Serum (25-OH) Vitamin D level (ng/ml) among the studied groups:-

Table (6) shows comparison between serum 25-OH vitamin D level in children on antiepileptic drugs and the control group.

Mean serum 25-OH Vitamin D in Valproic acid treated group was (16.06+11.20), in carbamazepine treated group was (17.63+4.12), in Levetiracetam treated group was (37.98+10.45), in topiramate treated group was (34.88+9.45) and in the control group was (38.31+10.05).

There was significant decrease in the mean serum 25-OH Vitamin D level in both valproic acid treated group (p1<0.001) and carbamazepine treated group (p2<0.001) when compared with the control group while there was no significant difference in mean 25-OH VitD between levetiracetam treated group (p3=0.99), topiramate treated group (p4=0.40) and the control group.

Table (6): Serum 25-OH Vit D (ng/ml) level among the studied groups

Serum 25 OH Vit D (ng/ml)	Valproic acid Treated Group (n=30)	Carbamazepine Treated group (n=30)	levetiracetam Treated group (n=20)	Topiramate Treated group (n=20)	Control (n=50)
Range	11.2 – 23.7	11.2 – 16.3	25.8 – 63.5	24.4 – 60.8	24.67 – 60.70
Mean ± SD	16.06 + 11.20	17.63 + 4.12	37.98 + 10.45	34.88 + 9.45	38.31+ 10.05
Median	14.35	17.70	35.70	33.15	36.20
F	63.32				
P	0.001*				
Sig. bet. Groups	p_1<0.001*, p_2<0.001*, p_3=0.99, p_4=0.40				

F, p: F and p values for **ANOVA test**, Sig. bet. groups was done using **Post Hoc Test (LSD)**
P1: Valproic treated Group vs Controls.
P2: Carbamazepine treated Group vs Controls.
P3: Levetiracetam treated Group vs Controls.
P 4: Topiramate treated Group vs Controls.
*: Statistically significant at $p \leq 0.05$

Correlation between the duration of treatment with different antiepileptic drugs and serum level of 25 OH vitamin D:-

Table (7) shows inverse correlation between serum 25-OH vitamin D level and the duration of treatment with valproicacid and carbamazepine. The longer the duration of treatment with each of them, the more significant the decrease in Serum level of 25-OH vitamin D.

While there was no significant correlation between the duration of treatment with levetiracetam and topiramate and the mean level of 25- OH Vitamin D.

Table (7): correlation between the Serum 25-OH Vit D (ng/ml) level and the duration of the treatment according to the type of antiepileptic drug received among the studied groups

Serum 25 OH Vit D (ng/ml) level	Duration (month)	
	r	P
Valproic acid Treated Group	-0.89	0.001 *
Carbamazepine Treated group	-0.87	0.001 *
levetiracetam Treated group	-0.28	0.23
Topiramate Treated group	-0.16	0.49

r: spearman coefficient correlation
*: Statistically significant at $p \leq 0.05$

4. Discussion

This study was performed to evaluate the effect of AEDs on vitamin D and calcium status in children with idiopathic epilepsy receiving antiepileptic drugs as carbamazepine, valproic acid, levetiracetam and topiramate.

Understanding the role of vitamin D in various health functions has increased in the past few years. Beyond its well-known role in bone health vitamin D is implicated in diverse functions such as cardiovascular health, tumor prevention,

immunological function as well as glucose metabolism (5)

Deficient levels of vitamin D have been associated with several brain disorders including multiple sclerosis, Alzheimer and Parkinson diseases, autism, schizophrenia and cerebrovascular disorders. Yet as compared much less attention has been paid to epilepsy, the second major neurological disorder. (6)

In the present study, serum level of 25(OH) Vitamin D was measured in 100 epileptic children, 30 of them treated with Valproic acid, 30 treated with Carbamazepine, 20 treated with Levetiracetam and 20 treated with Topiramate for at least one year and compared with 50 healthy children of the same age and sex.

Patients treated with both valporate and carbamazepine had lower vitamin D level than the control.

On the other hand, children treated with Levetiracetam and Topiramate had normal levels of vitamin D when compared with the control group.

The results of this study agree with **Fong C.Y. et al 2016, (7)** who made cross-sectional study of ambulant children with epilepsy on long-term AEDs for >1 year seen in three tertiary hospitals in Malaysia from April 2014 to April 2015 where a total of 244 children (146 male) participated in the study with ages ranged between 3.7 and 18.8 years (mean 12.3 years). Vitamin D deficiency was identified in 55 patients (22.5%), and a further 48 (19.7%) had vitamin D insufficiency.

Also this study agrees with **Sreedharan M., et al,2018. (8)** who assessed the effect of monotherapy with Carbamazepine (CBZ) and Sodium valproate (VPA) on serum 25-OH vitamin D levels in children with epilepsy compared to controls. They made the study on (56) Children with epilepsy aged 2 to 13 years. (28) children of them were on monotherapy with CBZ and (28) children were on VPA for at least 6 months; 109 age-matched controls from a nearby day-care centre and school and showed that serum 25-OH vitamin D levels are significantly low in children on carbamazepine or valproate monotherapy.

Also the results of this study agree with **Lee Y. G. et al, 2015, (9)** who had also studied vitamin D level at the start of antiepileptic drugs and at 6 to 12-month intervals in children with epilepsy taking antiepileptic drugs in Pusan National University Children's Hospital. A total of 143 children (103 boys and 40 girls) with the mean age of 7.4 ± 5.4 years were included. The mean follow-up duration was 1.8 ± 0.8 years. They found that high proportion of these children on antiepileptic drugs had hypovitaminosis D and a significant decrease between vit D level at the start of treatment and at the last follow-up.

Also this study agrees with **Kumandas S. et al, 2006. (10)** who made a study on ambulatory epileptic patients who were divided into two groups. Thirty-three patients (group 1; 17 boys, 16 girls; mean age: 8.8) were treated with valproic acid and 33 patients were treated with carbamazepine (group 2; 20 boys, 13 girls; mean age: 9.7). The control group consisted of 22 healthy children (13 boys, 9 girls; mean age: 8.9), who were age- and sex-matched with the patient groups and found that Serum 25-hydroxyvitamin D of the carbamazepine-treated group was significantly lower than the other groups.

The study results also agree with **Koo DL. et al, 2013. (11)** They made a study on drug-naïve, sixty-one patients with recent onset epilepsy (24 female, 37 males; mean age: 31.0 ± 13.1 years). They measured calcium, phosphorus, bone alkaline phosphatase, parathyroid hormone, vitamin D3 levels and bone density measurements with DEXA method before and after Levetiracetam administration of mean duration 14.16 ± 3.36 months and concluded that Levetiracetam monotherapy may have no harmful effect on bone strength and metabolism after one year of treatment.

Also, the results of this study agree with **Nicolaidou P. et al, 2006. (12)** who found that carbamazepine and sodium valproate can cause hypovitaminosis D in children after a study done on 51 ambulatory epileptic children who were followed during the first year of the study and in 25 and 6 children during the second and third year, respectively. The control group consisted of 80 healthy children.

On the other hand, the results of this study were contradictory to the results obtained by **Turan M. I., et al, 2014. (13)** that aimed to examine the effects of valproic acid (VPA), carbamazepine (CBZ), and phenobarbital (PB) -AEDs frequently used in childhood- on bone mineral metabolism and thyroid function tests. In their study, children monitored with a diagnosis of idiopathic epilepsy by the pediatric neurology clinic, using AEDs for at least 6 months and with episodes under control, were included. Patients were divided into groups on the basis of the drugs used. Thyroid function tests and 25-hydroxyvitamin D or 25(OH) vit. D levels were measured from blood specimens. They found that Valproic acid, Carbamazepine, and phenobarbital have no effect on vitamin D levels.

The results of this study are contradictory with the results obtained by **Serin HM., et al, 2015. (14)** In that study, Fifty-nine patients (32 males, 27 females; mean age: 8.6 ± 4.6 years) and a control group (13 males, 7 females; mean age: 7.6 ± 3.3 years) were included. The patients were receiving necessarily the same antiepileptic drugs (AEDs) for at least two years, and none of the patients had mental retardation or cerebral palsy. The patients were divided into three

groups: group 1 (patients receiving levetiracetam, n = 20), group 2 (patients receiving carbamazepine, n = 11), and group 3 (patients receiving valproic acid, n = 28) and a control group with matched age and gender. They found that, the differences between P, PTH, ALP, Ca BMD results, and vitamin D levels of the children in all four groups were not statistically significant i.e. Valproic acid and carbamazepine had no significant effect on Vitamin D level.

But according to the Levetiracetam treated group, the results of this study agree with **Serin HM. et al., 2015. (14)** as they found also that Levetiracetam has no significant effect on Vitamin D level in children with idiopathic epilepsy.

Also, The results of this study are contradictory to the results obtained by **Rauchenzauner M., et al, 2010**. **(15)** In their study, eighty‐five children (38 males, 47 females) were treated with valproate and 40 children (28 males, 12 females) were treated with other AEDs (lamotrigine, or oxcarbazepine), comprising the non‐valproate group. Forty‐one healthy children (29 males 12 females; mean age 12y 1mo) served as a control group. 25‐hydroxyvitamin D, calcium, phosphate were measured. They found that none of the studied children was vitamin D deficient which means that valproic acid has no effect on vitamin D level in children with idiopathic epilepsy.

Regarding the effect of topiramate and levetiracetam on vitamin D level, the results of this study are also contradictory with the study done by **Teagarden, et al 2014. (16)** who conducted an observational study on epilepsy patients treated by two clinicians at the Emory University Epilepsy Center from 2008 to 2011 in order to determine the frequency of low vitamin D levels and possible differential antiepileptic drug risks. Vitamin D levels were obtained from 596 patients with epilepsy categorized into 3 groups: enzyme inducing anti-epileptic drugs (EIAEDs) e.g., carbamazepine, phenobarbital, phenytoin, primidone, Weak (EIAEDs) e.g., oxcarbazepine and topiramate since these AEDs produce weaker enzyme induction which is probably significant at higher dosages, or Non-EIAEDs e.g., gabapentin, lamotrigine, levetiracetam. They found that Topiramate and levetiracetam also cause vitamin D deficiency. But the results of this study agrees with them regarding carbamazepine and valporate treated group. They concluded that Vitamin D deficiency was present in 54% of enzyme-inducing and 37% of non-enzyme-inducing antiepileptic drugs groups.

The results of this study are also contradictory with **Heo., et al, 2011. (17)** who studied the effect of topiramat on bone mass and metabolism in premenopausal women with epilepsy. Thirty‐six women on long‐term (at least 1 year) topiramate monotherapy were compared with 36 women taking carbamazepine, 32 women taking valproate, and 36 age and sex‐matched controls. Subjects completed bone mineral density (BMD) studies. Serum was analyzed for indices of bone metabolism and found that serum calcium concentrations were significantly lower in patients receiving topiramate than in those receiving valproate and controls.

Limitations

The main limitation of this study is that this was a cross-sectional study, and basal biochemical analysis was not measured before anticonvulsant use.

Another limitation is that bone mineral density was not evaluated. Dual-energy X-ray absorptiometry is considered the “gold standard” for the assessment of bone mineral density, but the short duration of antiepileptic therapy and the risk-benefit analysis does not justify to perform bone mineral density measurements in the patients included in this study.

Conclusion

In the present study there was significant decrease in serum calcium and phosphorus level in patients treated with valproic acid and carbamazepine as monotherapy for at least one year in comparison with the control group while there was no significant difference between serum calcium and phosphorus levels between patients treated with levetiracetam and topiramate as monotherapy for at least one year and the control group.

Regarding alkaline phosphatase and parathormone level, there was significant increase in their serum level in Valproic acid and carbamazepine treated groups in comparison with the control group while there was no significant difference between levetiracetam and topiramate treated groups and the control.

Also regarding serum 25-OH vitamin D level, this study showed significant decrease in its level in both valproic acid and carbamazepine treated groups when compared with the control group while there was no significant difference between levetiracetam and topiramate treated groups and the control group.

Also, there was inverse correlation between the duration of treatment with valproic acid and carbamazepine and the mean level of 25-OH Vitamin D. The longer the duration of treatment, the lower the mean level of vitamin D.

From this study we conclude that vitamin D deficiency is relatively common in children with epilepsy -without abnormal underlying conditions- who had received valproate or carbamazepine as a monotherapy for at least twelve months.

Also this study showed inverse correlation between serum 25-OH Vitamin D level and duration

of treatment with valproic acid and carbamazepine. The longer the duration of treatment, the more significant decrease in mean 25-OH Vitamin D level.

References:

1. Marcuccilli CJ. Vitamin D deficiency in pediatric epilepsy. Journal of Pediatric Epilepsy. 2013;2:199-208.
2. Baek J.H, Seo Y.H, Kim G.H, Kim M.K, Eun B.L. Vitamin D levels in children and adolescents with antiepileptic drug treatment. Yonsei medical journal. 2014;55:417-21.
3. Ramya S, Anitha C, Ravi M. A study of vitamin-D status in epileptic children in age group of 2-15 years. International Journal of Advances in Medicine. 2017;3:319-23.
4. Fisher RS, Cross JH, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522-30.
5. Holick MF. Vitamin D deficiency. New England Journal of Medicine. 2007;357:266-81.
6. Cannell JJ, Grant WB. What is the role of vitamin D in autism? Dermato-endocrinology. 2013;5:199-204.
7. Fong CY, Kong AN, Poh BK, et al. Vitamin D deficiency and its risk factors in Malaysian children with epilepsy. Epilepsia. 2016;57:1271-9.
8. Sreedharan M, Devadathan K, Kunju PM, et al. Vitamin D Deficiency in Ambulant Children on Carbamazepine or Sodium Valproate Monotherapy. Indian pediatrics. 2018;55:307-10.
9. Lee Y-J, Park KM, Kim YM, et al. Longitudinal change of vitamin D status in children with epilepsy on antiepileptic drugs: prevalence and risk factors. Pediatric neurology. 2015;52:153-9.
10. Kumandas S, Koklu E, Gümüs H, Koklu S, et al. Effect of carbamezapine and valproic acid on bone mineral density, IGF-I and IGFBP-3. Journal of pediatric endocrinology & metabolism: JPEM. 2006;19:529-34.
11. Koo DL, Joo EY, Kim D, Hong SB. Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. Epilepsy research. 2013;104:134-9.
12. Nicolaidou P, Georgouli H, Kotsalis H, et al. Effects of anticonvulsant therapy on vitamin D status in children: prospective monitoring study. Journal of child neurology. 2006;21:205-10.
13. Turan MI, Cayir A, Ozden O, Tan H. An examination of the mutual effects of valproic acid, carbamazepine, and phenobarbital on 25-hydroxyvitamin D levels and thyroid function tests. Neuropediatrics. 2014;45:016-21.
14. Serin HM, Koç ZP, Temelli B, Esen İ. The bone mineral content alterations in pediatric patients medicated with levetiracetam, valproic acid, and carbamazepine. Epilepsy & Behavior. 2015;51:221-4.
15. Rauchenzauner M, Griesmacher A, Tatarczyk T, et al. Chronic antiepileptic monotherapy, bone metabolism, and body composition in non-institutionalized children. Developmental Medicine & Child Neurology. 2010;52:283-8.
16. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. Epilepsy research. 2014;108:1352-6.
17. Heo K, Rhee Y, Lee HW, et al. The effect of topiramatemonotherapy on bone mineral density and markers of bone and mineral metabolism in premenopausal women with epilepsy. Epilepsia. 2011;52:1884-9.

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