EVALUATION OF VITAMIN D STATUS IN CHILDREN WITH REFRACTORY EPILEPSY

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ABSTRACT

Background: *Vitamin D deficiency has been reported in children using antiepileptic drugs. Multiple antiepileptic drugs may conceivably increase the risk of vitamin D deficiency.*

Aim of the work: *to determinate the vitamin D status and risk factors for vitamin D deficiency in children with refractory epilepsy.*

Patient and method: *Fifty refractory epileptic patients and fifty matched healthy subject participated in the study collected by simple random methods. This study was carried out in both General pediatric and Neurology Outpatient Clinics in Bab El-Sheria Hospital, Cairo, Egypt. In the period from April 2019 to November 2020.Measurements of serum levels of 25-OH Vitamin D, calcium, phosphorus, parathormone, and alkaline phosphatase were done for included subjects.*

Results: *Serum 25-OH Vitamin D, calcium and phosphorus were significantly lower, whereas serum parathormone and alkaline phosphatase were significantly higher in epileptic children compared to control subjects. Epileptic children treated with antiepileptic drugs which increase catabolism of vitamin D by inducing CYP 450 had significantly lower serum (calcium, phosphorous, and vitamin D) values compared to those receiving non enzyme inducing CYP 450.*

Conclusion: *The prevalence of vitamin D deficiency is common in children with epilepsy treated with antiepileptic drugs which increase catabolism of vitamin D by inducing CYP 450 as carbamazepine, Phenytoin or phenobarbital.*

Recommendation: *Hence vitamin D status of children treated with these drugs should be regularly monitored and vitamin D supplements should be considered on an individual basis.*

Keywords: *Children, Refractory epilepsy, Vitamin D.*

INTRODUCTION

Epilepsy is a chronic no communicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.[1]

Epidemiological studies on drug-resistant epilepsy have until recently been limited by lack of a standardized definition. In 2012, a taskforce appointed by the International League against Epilepsy (ILAE) proposed an operational definition for drug resistant epilepsy as "the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[2]

Vitamin D is an essential nutrient in humans; it is produced by the body through exposure to the sun (the primary source of vitamin D), or more precisely, to mild ultraviolet B (UVB) light. Other sources of vitamin D include food and dietary supplements.[3]

Chemically, vitamin D2 was first characterized in 1932, and vitamin D3 was characterized in 1936. Currently, vitamin D is known as a hormone that regulates calcium-phosphorus homeostasis and protects the integrity of the skeletal system.[4] Vitamin D levels are influenced by many factors, including the season, period of sun exposure, time of the day, latitude, and use of sunscreen, clothing, skin color, body weight, and medical conditions.[5]

The association between vitamin D, antiepileptic drugs (AEDs) and poor bone health in epileptic patients is known[6]. In children this issue is particularly important because they use AEDs during the time of maximum bone mineralization[7]. Seizures, neuro motor dysfunction, long term treatment with medications affect bone health of epileptic children and vitamin D deficiency creates additional risk for poor bone health[8].

AEDs increase the catabolism of vitamin D via the induction of cytochrome P450 system[9]. Non-enzyme inducing AEDs (e.g., valproic acid) have also been associated with poor bone health[10].

Poly pharmacotherapy in epileptic patients is a risk factor for vitamin D deficiency. In addition to poly pharmacotherapy, children with refractory epilepsy might have additional risk factors like cognitive impairment and psychiatric disturbances due to frequent seizures, motor dysfunction related immobility and frequent respiratory infections in which vitamin D may be beneficial.[11]

PATIENTS AND METHODS

This case-control study was carried on 100 subjects (50 Refractory epileptic children (group A) and 50 healthy matched subjects (group B)) they were collected by simple random methods.

Refractory epileptic children were subdivided into two subgroups:

- **Group (A1**) treated with AEDs which increase catabolism of vitamin D by inducing CYP 450 e.g. carbamazepine, Phenytoin or phenobarbital (N= 29).
- **Group (A2)** treated with AEDs which non inducing CYP 450 e.g. Valproate sodium, Levetiracetam, Lamotrigine, Topiramate, Clonazepam (N=21).

This study was carried out in both General pediatric and Neurology Outpatient Clinics in Bab El-Sheria Hospital, Cairo, Egypt. In the period from April 2019 to November 2020.

Inclusion criteria:

The inclusion criteria for the children (group A):

- Age: above one year old till sixteen years old.
- Inadequate seizure control despite appropriate therapy with at least 2 AEDs in maximally tolerated doses for 1 years.

Exclusion criteria:

The exclusion criteria for the children:

- Patients with age below one year or above sixteen years old.
- Children who were already on vitamin D supplementation at the time of study.
- Children diagnosed as rickets before study.
- Patients suffering from any systemic chronic illness other than epilepsy.

For all included patients, the following was done:

- **Complete history:** A complete history taking with stress on vitamin D supplementation and AEDs intake (types&duration).
- **Clinical evaluation:** A complete clinical evaluation includes (Anthropometric measurements and a clinical examination of the nervous system in particular and examination of the rest of the body's systems in general).
- **Laboratory evaluation:**
    1. Serum 25-hydroxy vitamin D (25-OHD).
    2. Serum calcium (Ca).
    3. Serum Phosphorus (PO4).
    4. Parathyroid hormone (PTH).
    5. Alkaline phosphatase (ALP).

Ethical considerations:

1. Approval of the ethical committees of Al-Azhar faculty of medicine & pediatric department was obtained before the study.
2. Informed consent was obtained from parents of all included children.
3. The aim of the study & all investigations as well as the risks & benefits of study have been explained to parents of the patients.
4. The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.
5. All data of patients & results of study are confidential & patients have the right to keep it.
6. The patient has the right to withdraw from the study at any time.

Statistical analysis of data:

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 25 (SPSS Inc, USA). For quantitative data, the mean and standard deviation (SD) were calculated. Independent t-test was used as a test of significance. Qualitative data were presented as number and percentages, chi square ($\chi 2$) was used as a test of significance. For interpretation of results of tests of significance, significance was adopted at $P \leq 0.05$.

RESULTS

Table (1): Demographic data of both studied groups

Variables \ Groups		Refractory group (A) N=50	Control group (B) N=50	Independent t-test		Significance
				T	P-value	
Age (months)	Mean ±SD	67.5±41.9	71.5 ± 46.6	0.444	0.657	NS
Body weight (kg)	Mean ±SD	22.1± 9	21.1 ± 9.8	1.035	0.303	NS
Height /length (cm)	Mean ±SD	107.6±22.4	109.9 ± 21.6	0.526	0.600	NS
BMI	Mean ±SD	15.5 ± 1.3	16.4 ± 1.12	3.532	0.001	HS
Sex				Chi- square test		
				X^2	P-value	NS
	Male	28(56%)	30(60%)	0.164	0.685	
	Female	22(44%)	20(40%)			
residence	Rural	24(48%)	18(36%)	1.478	.224	NS
	Urban	26(52%)	32(64%)			
+Family history	+ve	10(20%)	3(6%)	4.332	.037	NS
	-ve	40(80%)	47(94%)			

This table shows that there is a highly statistically significant deference between group (A) and group (B) regarding BMI. While no statistically significant difference was found between the two studied group regarding age, sex, weight, height, residence and family history.

Table (2): Comparison of laboratory results in both studied group

Serum level \ Group		Refractory group (A) N=50	Control group (B) N=50	Independent t-test		Significance
				T	P-value	
25 (OH) vitamin D	Mean ±SD	23.5 ±8.7	33.4 ±11.1	4.598	0.000	HS
	Range	27	50			
Ca+ (mg/dl)	Mean ±SD	8.2±1	8.9 ± 0.9	3.311	0.001	HS
	Range	4	3.7			
Po4 (mg/dl)	Mean ±SD	3.76 ±0.76	4.22 ±0.74	2.976	0.004	HS
	Range	3.4	2.7			
ALP (mg/l)	Mean ±SD	250.2 ±107.38	167.46 ±88.92	3.738	0.000	HS
	Range	293	267			
PTH (pg/ml)	Mean ±SD	65.21 ±22.54	44.81 ±20.75	4.221	0.000	HS
	Range	70	74.4			

This table shows that there was a statistically highly significant difference between the two groups as regarding 25 (OH) vitamin D, Ca+, Po4, ALP and PTH.

Table (3): Comparison between the two studied groups regarding 25(OH) vitamin D levels

25 (OH) vitamin D \ Group	Refractory group(A) N=50		Control group(B) N= 50		Chi-square test		Significance
	No.	%	No.	%	X^2	P-value	
Deficient (<20 ng/mL**)**	27	54%	10	20%	18.19	0.000	**HS**
Insufficient (20-30 ng/mL**)**	10	20%	6	12%			
Sufficient (>30 ng/mL**)**	13	26%	34	68%			

This table shows that there was a statistically highly significant difference between group (A) and group (B) as regarding 25 (OH) vitamin D degrees.

Table (4): Comparison between refractory subgroups regarding laboratory finding

Groups / Serum level		Enzyme inducing (A_1) N = 29	Non-enzyme inducing (A_2) N = 21	Independent t-test		Significance
				T	P-value	
25 (OH) vitamin D	Mean ± SD	18.78±4.29	30.15± 9.08	4.931	0.000	HS
	Range	20	24.5			
Ca+ (mg/dl)	Mean ± SD	7.73±.68	8.86 ±1.04	4.309	0.000	HS
	Range	2.6	3.2			
Po4 (mg/dl)	Mean ± SD	3.47±.67	4.16±.71	3.382	0.001	HS
	Range	3.4	2.3			
ALP (mg/l)	Mean ± SD	302.55 ±84.3	177.95±94.0	4.039	0.000	HS
	Range	283	248			
PTH (pg/ml)	Mean ± SD	75.52±17.73	50.98±20.93	3.592	0.001	HS
	Range	62	65			

This table shows that there was a statistically highly significant difference between group (A1) and group (A2) regarding 25 (OH) vitamin D, Ca+, Po4, ALP and PTH.

Table (5): Comparison between refractory subgroups and control group regarding 25 (OH) vitamin D level

Groups / Serum level		Refractory group (A)		Control (B) N=50	One Way ANVOA test		
		Enzyme inducing (A_1) N=29	Non enzyme inducing (A_2) N=21		F	P-value	Significance
25 (OH) vitamin D (ng/ml)	Mean ± SD	23.5±8.7	30.15± 9.08	33.4±11	19.3	0.000	HS
	Range	27	24.5	50			
Post Hoc Analysis							
Group(A_1)		Group (A_1)		Group (**B**)			

vs. Group (**B**)	**vs.** Group (**A_2**)	**vs.** Group (**A_2**)
0.000	.001	0.377

This table shows that 25(OH) vitamin D level have statistically significant decrease in group (A1). Post Hoc test shows that 25 (OH) vitamin D level was deficient in group (A1) when compared to group (B) and in group (A2) respectively ($p<0.05$), while no statistically significant decrease in group (A2) when compared to group (B) ($p>0.05$).

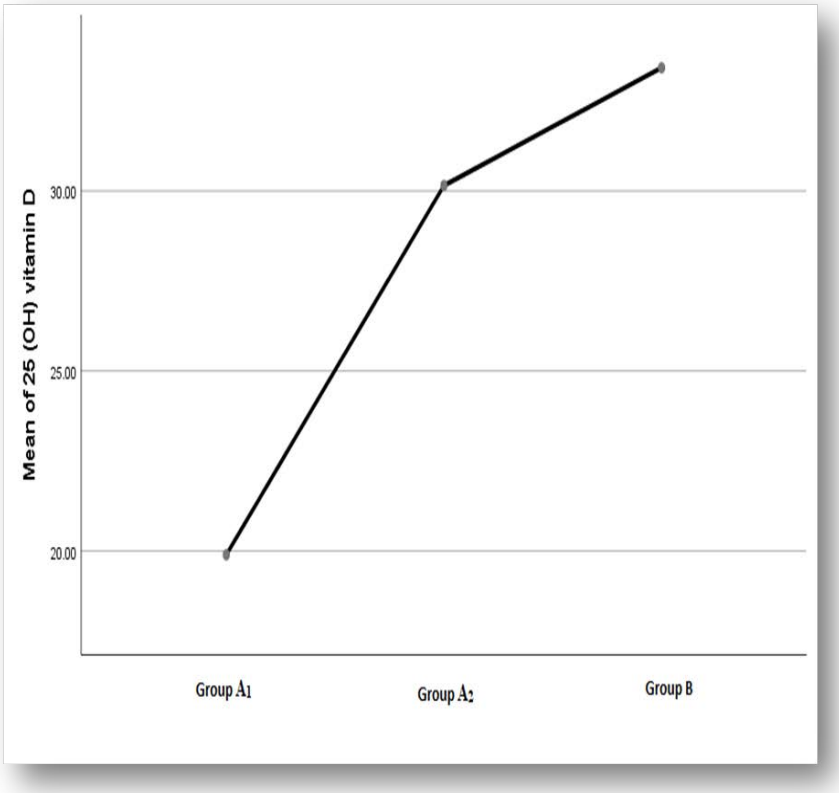

Figure (1): Comparison between Refractory subgroups and control group regarding mean of 25 (OH) vitamin D

Table (6): Correlation between 25 (OH) vitamin D levels and duration of AEDs treatment in refractory subgroups

Duration of AEDs usage		25 (OH) vitamin D level (ng/ml)			Kruskall-Wallis test		Significance
		Mean ± SD	Range	Median (IQR)	K	P-value	
Enzyme inducing (A_1) N=29	24m<	26.8± 7.9	18	29	6.527	0.038	NS
	24-48	18.8±3.7	11	181			
	48>	17.5±2.5	10	17			
Non enzyme inducing (A_2) N =21	24m<	28.22± 8	19.1	27	0.101	.951	NS
	24-48	30.33±8.6	22	29.2			
	48>	30.8±10.5	24.5	37.3			

This table shows that there is no statistically significant difference between 25(OH) vitamin D level and the duration of AEDs usage among the refractory subgroups respectively ($p>0.05$).

DISCUSSION

Epilepsy is one of the most prevalent neurological disorders of childhood and most of the children with epilepsy require long-term therapy with antiepileptic drug[12].

Refractory epilepsy can be defined as inadequate seizure control despite appropriate medical therapy with at least 2 AEDs in maximally tolerated doses for at least 18 months- 2 years or adequate seizure control with unacceptable drug-related side effects[13]. About 30 % of patients suffer from drug-resistant epilepsy[14].

Vitamin D plays several roles in modulation of cell proliferation, differentiation, neurotransmission and immune response in the central nervous system, In addition, vitamin D plays an important role in the regulation of calcium homeostasis and nerve excitability[15].

Anti-epileptic drugs may have some complications on bone and vitamin D metabolism[8].

Our aim in this study was to evaluate vitamin D status and risk factors for vitamin D deficiency in children with refractory epilepsy.

In our study regarding to demographic data we found that: In group A (refractory group) the mean age (months) was (67.5±41.9) vs. (71.5 ± 46.6) in group B (control group), (p= 0.657). And the percent of both male and female sex was (56% males and 44%females) in group A, and (60% males and 40%females) in group B (p= 0.685) With no statistical significant difference between the three studied groups.

Our findings are in agreement with those of **Jaydip et al. (2017)** who reported that there was no statistical difference regarding demographic data (age and gender) among the studied groups[16]. Also **Jung et al. (2014)** reported that there was no significant difference regarding age and sex in the studied groups of his study[17].

This study revealed a statistically significant difference in the serum level of laboratory finding between refractory patients and control group. Serum calcium, phosphorus, and vitamin D were significantly lower, whereas serum alkaline phosphates and parathormone were significantly higher in patients compared to controls. This goes in agreement with most previous studies **(Oner et al. 2004**; **Hamed et al. 2014**; **Pack, 2004**; **Mintzer 2010** and **Verrotti et al. 2010)**.[18, 19,20,21,22]

The present study established that the mean 25-hydroxyvitamin D levels was significantly lower in refractory epileptic children (23.5±8.7) ng/ml compared to controls (33.4±11.1) ng/ml (P<0.0001).Similar to a study of Malik et al. (2014) the mean level of 25-hydroxyvitamin D was lower among cases (28.79 ± 33.85) in contrast to controls (mean 47.62 ± 46.16)[23]. However, some studies have found no relationship between deficiency of 25-hydroxyvitamin D and epilepsy **(Pack, 2003**; **Babayigit et al. 2006** and **Razazizan et al. 2013)**[24, 25, 26].

Voudris et al., (2005) and **Babayigit et al., (2006)** found no significant association of calcium levels with epilepsy[25, 27].

This study revealed a statistically significant difference in the serum level of laboratory finding between group A1 and group A2. Serum calcium, phosphorus, and vitamin D were significantly lower, whereas serum alkaline phosphates, and parathormone were significantly higher in group (A1) compared to group (A2).This goes in agreement with most previous studies **(Pack et al., 2004**; **Feldkamp et al. 2000**; **Farhat et**

al. 2002 and **Ecevit et al., 2004)**.[28,29,30,31]

Enzyme inducers have several mechanisms which affect vitamin D, calcium, and phosphorus metabolism than enzyme inhibitors. They induce CYP 450 and pregnane X receptor (PXR) activation which in turn increases catabolism of vit. D, with subsequent decrease in serum calcium and phosphorus level as well as secondary hyperparathyroidism. This increases bone turnover with subsequent increase in alkaline phosphatase level as a marker of bone resorption.[32]

On the contrary, **Kafali et al. (1999)** failed to find significant decrease in serum calcium and phosphorus levels with the use of enzyme-inducing AEDs in comparison to non-enzyme inducers[33].

The present study established that mean 25-hydroxyvitamin D levels was significantly lower in group (A1) (18.78±4.29) compared to group (A2) (30.15± 9.08) (P<0.0001). In similar a study, **Eptesam et al. (2018)** found that the mean level of 25-hydroxyvitamin D was lower among cases (18.7 ± 6.1) in contrast to controls (27.9 ± 6.2)[34].

However, some studies have found no relationship between deficiency of 25-hydroxyvitamin D and epilepsy **(Pack, 2003**; **Babayigit et al. 2006** and **Razazizan et al. 2013)**.[24, 25, 26]

In the current study we compare between enzyme inducing group (A1) and non-enzyme inducing group (A2) with control group (B), we found there was highly significance decrease in 25 (OH) vitamin D in group (A1) when compared with group (A2) and group (B). But there is no significant difference when comparing group (B) with group (A2). These finding agree with **Eptesam et al., (2018)**.[34]

However, some studies have found no relationship between deficiency of 25-hydroxyvitamin D and epilepsy **(Pack et al. 2003**; **Babayigit et al. 2006** and **Razazizan et al. 2013)**.[24, 25, 26]

Also in our study we found no correlation between 25-hydroxyvitamin D deficiency and duration of treatment with AEDs. These result agree with **Pack (2003)** and **Razazizan et al. (2013)**[24, 26]. But In another study, 49% acquired vitamin D3 insufficiency within 3 months of AEDs **Nicolaido et al., (2006)**. **Farhat et al., (2002)** noted that exposure to AEDs for more than

six month leads to vitamin D deficiency in 35%.[30, 35]

CONCLUSION

The prevalence of vitamin D deficiency is common in children with epilepsy treated with antiepileptic drugs that increase catabolism of vitamin D by inducing CYP 450 e.g carbamazepine, Phenytoin or phenobarbital.

We found no correlation between 25-hydroxyvitamin D deficiency and duration of treatment with AEDs.

RECOMMENDATION

- Vitamin D supplementation is mandatory for epileptic patients especially those treated with AEDs that inducing CYP 450.
- Periodic measurement of vitamin D is recommended for epilepsy patients even for those without skeletal manifestations to avoid other morbidities associated with vitamin D deficiency.
- Further longitudinal studies including large number of pediatric epileptic patients to assess the prevalence of vitamin D deficiency and its potential effects on the course and complications of the disease.

Study limitations:

The current study had the following limitations:

- The results were from a single medical Centre.
- Children whom parents refuse to participate in this study.
- Costs of laboratory studies especially 25(OH) vitamin D &PTH.

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تقييم مستوى فيتامين د في الأطفال الذين يعانون من مرض الصرع المعند

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مقدمة البحث: الصرع هو اضطراب عصبي شائع يصيب جميع الفئات العمرية. عالميا،حوالى 70مليون شخص مصابون بالصرع -اى مايعادل 0.7% من العبء العالمى لجميع الامراض- فى البلدان الناميه.

يحتاج مرضى الصرع الى ادويه طويلة الأمد مضاده للصرع .يرتبط الاستخدام طويل الأمد لهذه الادويه الى تمثيل غذائى غير طبيعى لمعادن العظام مما قد يؤدى الى هشاشة العظام وزيادة خطورة حدوث كسور بالعظام.الآليه الرئيسيه يبدو انها ترتكز على نقص فيتامين (د) لدى الاطفال الذين يستخدمون هذه الادويه.

يلعب فيتامين (د) دورا حيويا فى الحفاظ على التوازن بين الفسفور ومستويات الكالسيوم وكذالك التمثيل الغذائى.فيتامين (د) ضرورى ايضا لأنظمة الأعضاء بخلاف نظام الهيكل العظمى وقد ارتبط نقصه بزيادة خطر الأصابه بالعدوى وأمراض المناعه الذاتيه والسكرى

ومتلازمة التمثيل الغذائى والسمنه والربو وبعض الامراض العصبيه.

يعد العلاج الدوائى المتعدد فى مرضى الصرع المعند أحد عوامل الخطر لنقص فيتامين(د) .بالاضافه الى العلاج الدوائى المتعدد, قد يعانى الأطفال المصابون بالصرع المعند من عوامل خطر اضافيه مثلا الضعف الادراكى والاضطرابات النفسيه بسبب النوبات المتكرره والخلل الحركى المرتبط بعدم الحركه والتهابات الجهاز التنفسى المتكرره التى قد يكون فيتامين (د) مفيدا فيها.

الهدف من البحث: وقد كان الهدف من البحث الحالى هوا تحديد حالة فيتامين (د) وعوامل الخطر لنقص فيتامين (د) لدى الاطفال المصابين بالصرع المعند.

مواد وطرق البحث: وقد أجريت هذه الدراسة بالعياده الخارجيه لقسم طب الاطفال بمستشفى باب الشعرية الجامعى التابعه لجامعة الازهر بنين فى الفتره من ابريل 2019حتى نوفمبر 2020 على100 طفل منهم 50 طفل (28ولد و22بنت) مرضى بالصرع المعند تتراوح أعمارهم بين عام و 16عاما كمجموعه (أ) و 50طفل (30ولد و20بنت) من الأطفال الأصحاء يمثلون مجموعة ضابطة كمجموعه(ب).

وقد تم تقسيم المجموعة الاولى (مرضى الصرع المعند) إلى مجموعتين:

- المجموعة (أ1) وتشمل 29 طفل (16ولد و 13 بنت) يعانون من الصرع المعند ويعالجون بادويه متعدد للصرع تعمل على تحفيز انزيم السيتوكروم ب 450.
- المجموعة (أ2) وتشمل 21 طفل (12 ولد و9 بنات) والذين يعانون من من الصرع المعند ويعالجون بادويه متعدد للصرع لا تعمل على تحفيز انزيم السيتوكروم ب 450.

معايير الاشتمال:

- السن من 1 عام حتي 16 عام.
- عدم كفاية السيطره على النوبات على الرغم من العلاج المناسب الذى يحتوى على نوعين من الادويه المضاده للصرع (على الاقل) بجرعات عاليه يمكن تحملها لمده 1 عام.
- موافقه كتابية من القائم على رعاية الطفل بالمشاركه فى هذه الدراسه.

معايير الاستبعاد:

- الأطفال أقل من عام او اكبر من 16 عام في العمر.
- الاطفال الذين كانوا بالفعل على مكملات فيتامين د وقت الدراسه.
- الاطفال الذين تم تشخيص اصابتهم بالكساح قبل الدراسه.
- المرضى الذين يعانون من اى امراض مزمنه اخرى غير الصرع.
- الاطفال الذين يرفض اباؤهم المشاركه فى هذه الدراسه.

تم إجراء الآتى لكل طفل من هؤلاء الأطفال:

- أخذ تاريخ مرضى كامل.
- التقييم الإكلينيكى الكامل يشمل كل من (العلامات الحيوية والطول والوزن ,والفحص الاكلينيكى للجهاز العصبى خاصة وفحص باقى أجهزة الجسم عامه).
- أخذ عينة دم.

1. لقياس مستوى فيتامين (د) الذائب فى مصل الدم.
2. قياس نسبة الكالسيوم والفسفور بالدم.
3. قياس نسبة هرمون الغده الجار درقيه.

4. قياس نسبة انزيم الفوسفاتيز القلوى.

وبالتحليل الإحصائى للنتائج وجد أن:

بمقارنة نتائج المجموعات وجد ان نسبة فيتامين (د) ونسبة الكالسيوم والفسفور منخفضه عالترتيب فالمجموعه (أ) مقارنة بالمجموعه الضابطه (ب) بينما وجد ارتفاع فنسبة هرمون الغده الجار درقيه وانزيم الفوسفاتيز القلوى عالترتيب فالمجموعه (أ) مقارنة بالمجموعه الضابطه (ب).

هناك انخفاض احصائى ملحوظ في مستوى فيتامين (د) ونسبة الكالسيوم والفسفور عالترتيب فى المجموعه التى تحتوى ادوية علاج الصرع المعند على انزيم محفز للسيتوكروم ب 450 (أ1) مقارنة بالمجموعه (أ2) التى لا تحتوى ادوية علاج الصرع المعند على انزيم محفز للسيتوكروم ب 450.

كما وجد أيضا أن هناك ارتفاع فى نسبة هرمون الغده الجار درقيه وانزيم الفوسفاتيز القلوى عالترتيب فى المجموعه (أ1) مقارنة بالمجموعه(أ2).

كما كشفت دراستنا عن عدم وجود تأثير لنوع النوبة، أو بدايتها، أو تكرارها، أو مدة العلاج باستخدام الصرع على حالة فيتامين د.

نستخلص: من هذا البحث ما يلى:الأطفال الذين يعانون من الصرع المعند ويتداوون باكثر من دواء من ادوية الصرع يعانون من نقص فى فيتامين (د) والكالسيوم والفسفور وارتفاع فى نسبة هرمون الغده الجار درقيه وانزيم الفوسفاتيز القلوى عالترتيب خصوصا اذا كانت تحتوى هذه الادويه على انزيم محفز للسيتوكروم ب 450 مما قد يعرض هؤلاء الاطفال على المدى الطويل الى هشاشة العظام وتكرار تكسر العظام نتيجة لهشاشتها.

توصيات البحث:

- إضافة فيتامين (د) كمكمل بمثابة العلاج المساعد في الأطفال الذين يعانون من الصرع المعند.
- يوصى بالقياس الدوري لفيتامين د لمرضى الصرع حتى لمن ليس لديهم علامات مرضية مرتبطة بنقص فيتامين د.
- مزيد من الدراسات تشمل عدداكبر من الأطفال مرضى الصرع لتقييم انتشار نقص فيتامين د وتأثيراته المحتملة على مسار المرض ومضاعفاته.