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VITAMIN D DEFICIENCY IN CHILDREN WITH EPILEPSY TAKING VALPORT AND LEVETIRACETAM AS MONOTHERAPY

[1]Dr. Khush Bakhat, [2]Dr. Muhammad Naeem Saleem,[3]Dr. Sadia Noureen

[1]WMO, RHC, Jamke Cheema, Sialkot.

[2]MO, BHU 490GB, Tandlianwala, Faisalabad.

[3]WMO, BHU 34 SB, Sargodha.

Abstract:

The basic objective of this study is to analyze if "valproate" (VPA) and "levetiracetam" (LEV) as monotherapy may correlate with the deficiency of vitamin D in children affected with epilepsy.

The base of this study is on cross-sectional clinical (consisted on epilepsy aetiology, seizure kinds, level of drugs, dosage and AED treatment duration) and testing of blood (consisted on 25-OHD, calcium, phosphorus and PTH) study which established in epileptic 90 children (consisted on AED group: 31 children receiving LEV and 59 children receiving VPA) with a control group (healthy subjects of 244). The category of 25-OHD was as low (<20 ng/ml) or normal (>30 ng/ml) or borderline (20-29 ng/ml).

The VPA average dose was 20.7 ± 4.7 milligrams/kg/per day and the average dose of LEV was 24.1 ± 7.9 milligrams/kg/per day. VPA therapy mean duration was 2.5± 1.4 years and similarly the mean duration of LEV was 2.3 ± 1.6 years. In control group 25-OHD levels and mean calcium were typically higher ($p < 0.05$) and between 25-OHD and VPA there is negative correlation ($p < 0.01$) and the percentage of Vitamin D deficiency was ominously higher ($p < 0.05$) in LEV (35.5%) and in VPA (24.1%) as compared with control group (with 14%). A different analysis of logistic regression represented that LEV monotherapy (OR: 3.3, CI 95%: 1.5-7.5) and VPA monotherapy (OR: 1.9, CI 95%: 1.1-3.8) were related with high risk of deficiency of Vitamin D.

Accordingly, the vitamin D deficiency frequency is very common with epileptic children taking LEV or VPA. Therefore, the children status treated with LEV and VPA must be monitored on a regular basis and supplements of vitamin D must be considered on a personal basis.

Keywords: *Vitamin D Deficiency, Epilepsy, Valport, Levetiracetam, Monotherapy*

*** Corresponding author:**

Dr. Khush Bakhat,

WMO,

RHC, Jamke Cheema,

Sialkot.

QR code

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1.0 INTRODUCTION:

Vitamin D always plays important and multiple roles in cell differentiation, proliferation modulation, neurotransmission and in the immune response in the nervous system. Additionally, it also plays a highly important role in "calcium homeostasis and nerve excitability" regulation. It is true that anticonvulsant result basically reported in 1974 in those patients which were affected by low serum 25-OHD level and pharmacoresistant epilepsy. Hypovitaminosis D is basically an experienced global health issue. Gender, the season of serum collected year, skin pigmentation, geographical atmospheric conditions, urban residence, skin disease, obesity, cholestasis and chronic medications mostly associated with hypovitaminosis D (Fiedler et al., 2008).

Similarly, epilepsy is high neurological childhood disorder and mostly epilepsy affected children need long-term therapy while using AEDs (antiepileptic drugs). On the other hand, most of the classic antiepileptic drugs are hepatic P450 system inducers and it may basic reason for Vitamin D deficiency. Anyhow, AEDs with non-enzyme inducing also be related with hypovitaminosis D but the basic procedure for this may need further analysis. For instance, 25-OHD (level of 25-hydroxyvitamin D) and density of lower bone mineral has further been documented in epileptic children, specifically under cure with valproate (Galesanu, Grozavu and Alexandru, 2015).

The basic objective of this research is to analyze the role of (LEV) levetiracetam and (VPA) valproate as monotherapy specifically with the deficiency of vitamin D through epileptic children.

2.0MATERIAL AND METHODS:

2.1*Participants*

For this research 90 epileptic children (consisted of 51 girls and 39 boys) with a control group (consisted of 126 girls and 118 boys) were comprised in a cross-sectional analysis. The entire participant (boys and girls) experienced a blood testing and clinical examination in the duration starting from October 2013 till June 2014. Entire participants were further divided into three groups: first one named VPA group (in this group epileptic patient receiving "valproic acid", n =59), a second group named LEV group (in this group epileptic patients receiving "levetiracetam" n = 31) and final is the control group. All children were outpatients with no further motor insufficiencies who had received levetiracetam or valproic acid as monotherapy with at least a duration of twelve months. They do not receive any additional calcium supplements or vitamin D; also note that no patient had any mental retardation or hepatic, renal, metabolic, and skeletal or cerebral palsy disorders. Furthermore, no patient, as per this study, previously receives any other AED rather than their current drug.

On the contrary, the 244 healthy children of the control group are based with normal nutritional eminence: Body Mass Index Z-Score between (15^{th} percentile) -1.0 and (85^{th} percentile) + 1.0. Similarly, all healthy children came from outside consultations of several paediatric subspecialties and none of them had any bone health illness or any chronic pathology which means to decrease their body composition, growth or any other physical activity; they do not receive any medication (glucocorticoids or antiepileptic medication) and any calcium supplement of vitamin D.

2.2Anthropometry and clinical information

Every patient's information has been recorded; including clinical and epidemiologic data; such as age, sex, body max index Z-scores, study visit season, seizure types, residence, epileptic aetiology, any antiepileptic drugs (levetiracetam or valproic acid), level of drugs, dose, therapy duration. For classification and diagnosis, the currently proposed report of ILAE ("International League against Epilepsy") Commission on Classification and Terminology 2005-2009 has been concerned (Greer, 2009).

Juvenile phase was concerned in every respondent according to the criteria of Tanner; furthermore, patients were divided into two groups; the first one is a pre-pubertal group or school group according to Tanner Stage One and second is adolescent or pubertal group according to Tanner Stage Two-Five). Residence further considered as rural and urban. For "Body Mass Index" Z-scores values were considered through epidemiologic data which further delimited with application nutrition program based on a program by government health department for nutrition, hepatology, and gastroenterology (Harijan, Khan and Hussain, 2013).

2.3Biochemical Examination

During fasting, phosphorus calcium and alkaline phosphatase levels of plasma and were calculated by

consistent approaches. Furthermore, 25-OHD and PTH parathyroid hormone were calculated by chemiluminescence. The US Endocrine society benchmarks for vitamin D classification situation pertained. Deficiency of vitamin D was explored when levels of 25-OHD were lower than 20 ng/millilitre (<50nmol/L), considered that there is insufficiency of vitamin D when levels of 25-OHD were between 20-29 ng/millilitre (5-/75 nmol/L) and there is sufficiency of vitamin D when levels of 25-OHD overtake or reach 30 ng/millilitre (>75 nmol/L). Moreover, secondary hyperparathyroidism was described when the levels of Parathyroid Hormone Test serum surpassed 65 pg/ml (Durá-Travé et al., 2018).

2.4Statistical Assessment

Overall results are represented as means (M) and percentages (%) with standard deviations (SD) and 95% CI (confidence intervals). This study assessment was performed while using SPSS version 20.0 and some assistance also taken from the Chi-square test, "Pearson Correlation and Multiple Logistic Regression". It was also assumed that there are statistical significances when "p" was lesser than 0.05.

All parents or official and legal guardians of children were previously informed and delivered a verbal participation agreement before starting any analysis for this analysis in all cases. This study also followed all terms and conditions of "Ethics Committee for Human Investigation", (this study also performed under the ethical standards which stated in "1964 Helsinki Declaration with all further amendments" (John, 2012).

3.0 RESULTS:

Unknown seizures, focal and generalized number of patients was 53, 35 and 2 (as 58.9$, 38.9% and 2.2% respectively). The epilepsy aetiology was expected to be inherited specifically in 69 respondents which are 76.7%, structural-metabolic persists in 9 patients (10%) and unknown in 12 patient (which is 13.3% of a total number of patients).

Mean Dosage of VPA	20.7 ± 4.7 milligram/kg/daily (range: 12.3-37.7)
Mean Dosage of LEV	24.1 ± 7.9 milligram/kg/daily (range: 13.9-43.9)

Drug Levels of VPA	72.1 ± 25.9 mcg/ml (range: 17.3-144.7)
Drug Levels of LEV	7.7 ± 4.0 mcg/ml (range: 2.3-21.1)
Therapeutic VPA drug Levels	50-100 mcg/ml
Therapeutic LEV drug Levels	5-30 mcg/ml

Mean antiepileptic therapy duration with VPA was	2.5 ± 1.4 years (with the range of 1.3-4.5)
Mean antiepileptic therapy duration with LEV was	2.3 ± 1.6 years (range: 1.2-5.1)

Below mentioned table 1 represents and relates the presumed risk factor's distribution for hypovitaminosis D among control and AED groups. In this analysis, we can see that the girl's participant's percentage was expressively higher specifically in the VPA group while the boys' percentage was significantly greater in the LEV group. There was not expressive variance amount the distribution in age group, place of residence and season of blood sample relation.

Table 1. Distribution of presumed risk factors for hypovitaminosis D in AED groups and control group.

Items	VPA group (n = 59)	LEV group (n = 31)	Control group (n = 244)	p
Sex				
Boys	18 (30.5%)	21 (67.7%)	118 (48.4%)	0.003
Girls	41 (69.5%)	10 (32.3%)	126 (51.6%)	
Age Group				
School	30 (50.8%)	17 (54.8%)	135 (55.3%)	0.825
Adolescent	29 (49.2%)	14 (45.2%)	109 (44.7%)	
Season of study visit				
Autumn	20 (33.8%)	10 (32.3%)	93 (38.1%)	
Winter	19 (32.2%)	9 (29,0%)	82 (33.6%)	0.283
Spring	20 (33.8%)	12 (38.7%)	69 (28.3%)	
Residence				
Urban	36 (61%)	18 (58.1%)	170 (69,7%)	0.251
Rural	23 (39%)	13 (41.1%)	74 (30.3%)	

VPA: valproate. LEV: levetiracetam.

(Source: Durá-Travé et al., 2018)

Below mentioned table 2 represents and relates the clinical featured values and determination of biochemical between control and AED groups. 25-OHD and calcium levels were expressively greater in the control group, however, the level of phosphorus was expressively greater in AED groups. Accordingly, there was no important variance in Body Mass Index Z-Score, age, PTH and alkaline phosphatase in between multiple groups (Marcuccilli, 2015).

Table 2. Clinical and biochemical characteristics of the AED groups and control group (M ± SD).

Items	VPA group (n = 59)	LEV group (n = 31)	Control group (n = 244)	p
Age (yr)	10.15 ± 3.02	9.38 ± 3.83	9.64 ± 3.40	0.208
BMI (Z-score)	0.02 ± 0.59	0.17 ± 0.54	−0.05 ± 0.50	0.226
Calcium (mg/dL)	9.88 ± 0.33	9.87 ± 0.55	9.98 ± 0.35	0.041
Phosphorus (mg/dL)	4.91 ± 0.54	4.99 ± 0.69	4.54 ± 0.55	0.001
ALP (IU/L)	217.44 ± 81.23	246.30 ± 81.27	233.43 ± 77.99	0.261
PTH (pg/mL)	26.94 ± 9.41	28.21 ± 11.25	31.05 ± 16.18	0.093
25-OHD (ng/mL)	23.37 ± 9.11	22.64 ± 9.08	26.97 ± 7.09	0.037

VPA: valproate. LEV: levetiracetam. BMI: body mass index. ALP: alkaline phosphatase. PTH: parathyroid hormone. 25-OHD: 25-hydroxyvitamin D.

(Source: Durá-Travé et al., 2018)

There was a statistically momentous correlation found as ($p < 0.01$) between 25-OHD and Levels of VPA ($r = -0.442$). It was not observed that any correlation between LEV Levels and 25-OHD and the anticonvulsive therapy length (either for VPA or LEV). According to the MLR (Multiple logistic regression models) as shown in table 3 below, there are expressively odds of vitamin D deficit linked with urban residence, adolescent age and for both VPA and LEV AEDs. Other remaining variables (seizure types, sex, therapy duration and epilepsy aetiology did not properly contributed and purposely have been omitted (Pinemin, 2009).

Table 3. Multiple logistic regressions: factors associated with vitamin D deficiency.

Items	Vitamin D deficiency	
	OR (CI 95%)	(p)
Age group		
Children	1 (referent)	
Adolescents	1.9 (1.1–3.1)	0.013
Residence		
Rural	1 (referent)	
Urbana	1.6 (1.1–2.2)	0.010
AEDs		
Control Group	1 (referent)	
VPA	1.9 (1.1–3.8)	0.029
LEV	3.3 (1.5–7.5)	0.003

ADEs: antiepileptic drugs. VPA: valproate. LEV: levetiracetam.

(Source: Durá-Travé et al., 2018)

4.0DISCUSSION:

Some studies assessing and evaluating the status of vitamin D in those epileptic children which are medicated with latest antiepileptic drugs, it may also note that it is not initial report regarding the effectiveness of vitamin D status through LEV monotherapy. In this analysis the enrolled or participated individuals established a children's group with generalized or focal epilepsy, being unfamiliar aetiology predominant, and levetiracetam and valproate receiver as mono-therapy (Sen et al., 2016).

Furthermore, it has also been envisioned to establish both groups (control and AED group) as similar as probable to evade confounding issues that may further lead to the result's misinterpretation. Truthfully, there is no a motor deficit in any patient, cerebral palsy or mental retardation, and none had any other pathology which may affect body mass or composition, growth food ingestion or any other physical activity. Moreover, multiple factor's distributions are basically hypovitaminosis D related, like a pubertal stage, gender, pigmentation of the skin, serum collection season of the year, nutritional status and residence were identical between control and AED group (Sonmez et al., 2015).

Enzyme-inducing therapy of AED

There is multiple long-term antiepileptic poly-therapy or drug therapy such as primidone, phenobarbital, carbamazepine, and phenytoin. All these are well associated with the deficiency of Vitamin D and subsequently with a lessened bone health. Further, it

is also supposed that cytochrome 450-inducing AEDs catalyzes the conversion of 25-OHD through up-regulate the enzymes into polar motionless metabolites. While there is a reduction of calcium absorption as resulting decline shown in 1,25(OH)2 vitamin D, specifically with sequential secondary hyperparathyroidism, loss of accelerated bone and increase of reporting bone; moreover this would partially describe why persons who are agonizing from epilepsy have greater fractures risk than ordinary persons. Therefore, some studies also represented enzyme-inducing AEDs may further have a zero impact on the integrity of skeletal in the vitamin D deficiency absence. The possible system further suggested that there are declined intestinal calcium absorption, PTH resistance, deficiency of calcitonin and bone cell functionary direct effect of the drug (Sen et al., 2016).

All results found in this analysis must support that the treatment of VPA as monotherapy, specifically for the period of 12 months, is associated with importantly lower 25-OHD levels and serum calcium, with a high frequency of vitamin D deficiency as compared with control group (24.1% of VPA group were in vitamin D deficiency as compared with control group of 14%), finally there was no variance in PTH levels between both groups. Additionally, 25-OHD and VPA levels negative link has been observed and the assessment of multiple factors linked with hypovitaminosis D may assure that epileptic patients who are receiving valproate demonstrated a larger propensity towards deficiency of vitamin D as compared to control group (Greer, 2009).

5.0CONCLUSION:

It is observed in this analysis that deficiency of vitamin D is moderately common in epileptic children without any underlying abnormal status and conditions, specifically in those children who had received levetiracetam or valproate as monotherapy for the duration of at least one year. In prescribed patients, the status of vitamin D must be controlled regularly and there are more outdoor activities encouraged such as higher sun exposure, dairy products, fatty fish and many more. Of course, those children who have proven deficiency of vitamin D must receive other supplements with vitamin D.

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