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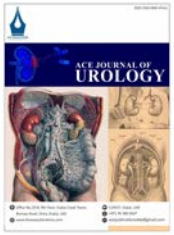

The Effects of Levetiracetam as an Antiepileptic on Vitamin D3 Levels in Iraqi Patients with a History of Epilepsy

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KEY WORDS
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Abstract
Levetiracetam, a newer antiepileptic drug (AED), is commonly prescribed due to its efficacy and safety profile. However, its effects on Vitamin D3 levels and bone health remain uncertain, particularly in long-term monotherapy. This study aimed to evaluate the effects of Levetiracetam monotherapy on Vitamin D3 levels, serum calcium and alkaline phosphatase (ALP) among Iraqi patients with epilepsy. This cross-sectional prospective study included 32 patients diagnosed with generalized or focal epilepsy. All patients received Levetiracetam monotherapy (1000-3000) mg/day for at least 6 months. Vitamin D3 levels, calcium levels and ALP values were analyzed. Results were presented in tables, percentages and correlations with dose and duration. The results showed that(35.3%) of patients had severe Vitamin D3 deficiency (<20) ng/ml, while (41.2%) had moderate Vitamin D3 deficiency (20-30) ng/ml. Normal Vitamin D3 levels (>30) ng/ml were observed in only (23.5%). A strong negative correlation (R=-0.54) was found between Vitamin D3 levels and Levetiracetam dose. Calcium deficiency was noted in (17.6%) of patients and (11.8%) had abnormal ALP levels. Levetiracetam monotherapy, particularly at higher doses, is associated with reduced Vitamin D3 levels and potential risks to bone health. Regular monitoring and supplementation are recommended to mitigate these effects.

INTRODUCTION

Epilepsy known as the patient has evidence of at least two or >tow seizures without identifiable cause, that render the patient with increasing chance of recurrent episodes and for that patients should start an anti-epileptic medications with too many options available to use with different modes of actions and different kinetics, patients many reach seizure free with just one AED by 50%-60% and increased by 10%-20% control and the third one my add 1%-3% only. Among newer AEDs, Levetiracetam has gained popularity due to its good adverse effect profile and a less interactions with other medications. However, AEDs, including older ones like carbamazepine and valproate, are known to induce Vitamin D deficiency through hepatic enzyme induction, affecting bone health, some studies showed that the new AEDs may also affect bone health in different ways[1-4]. Levetiracetam, marketed under the brand name Keppra, has been recognized for its favorable safety profile and tolerability compared to other traditional AEDs. Despite its widespread use, concerns have been raised regarding the potential effects of levetiracetam on bone health in general and vitamin D3 level specifically[5]. Levetiracetam exhibit its mode of action by binding to synaptic vesicle protein 2A (SV2A). Activation of pre-synaptic SV2A by this drug will reduce the neurotransmitter release. Its mechanism of action and the wide range of indications make it favorable for both health care providers and the patients as well[6]. Aslevetiracetam records increased chance of suicidal activity, the neurologist should be vigilant for this potential risk and monitors the patients regularly for this purpose and interviews the patient's partners or family[7,8]. Levetiracetam is absorbed rapidly with high (96%) bioavailability, the plasma peak concentration reaches within first hour, whatever the meals may delay the maximum concentration, but it does not affect the absorption[9]. Levetiracetam distribution: it is less than 10% protein bound and 60% of this drug is excreted by renal route.

Dosage Scale: The minimum dose of Levetiracetam is 500 mg and some elderly patients has benefit from low dose, increment by 250 mg to 500 mg every 1-2 weeks and the highest dose is 3000 mg per day. The starting dose in children is 20mg/kg daily in 2 divided doses and increased by 20 mg/kg every 1-2 week till a maximum 60mg/kg daily dose[10].

Common Adverse Effects of Levetiracetam Administration are:

- **Central Nervous System:** The common side effects are behavioral such as sedation, mood disturbance, restlessness, irritability, aggressiveness, headache, depression, memory loss, fatigue confusion, paresthesia and increased risk of suicidal ideation.
- **Cardiovascular (CVS):** Elevation of systemic blood pressure especially in pediatric age group.
- **Gastrointestinal (GI):** Nausea, anorexia, abdominal discomfort and sometimes vomiting.
- **Infections:** Upper respiratory tract infections registered in 7%-15% of patients.
- **Hypersensitivity Effects:** life-threatening reactions in rare percentage of patients, That may include anaphylactic reactions, angioedema, skin eruption, toxic necrosis of the epidermis and vasculitis.
- **Hematology:** decrease some blood products cell count[10].

The diagnosis of epilepsy relies on the history and semiology of events provided by the patients or witness. In addition to supportive investigations like an EEG (routine outpatients EEG), video EEG and brain-imaging. Detecting and understanding the events semiology, type of seizure according to ILAE updated classification and the triggering factors consider a paramount step in the diagnosis and treatment of epilepsy and help in expecting the prognosis as well[11-13]. The International League against Epilepsy (ILAEL) was used for classification of seizure[13-15].

MATERIALS AND METHODS

This cross-sectional prospective study included (32) patients whose ages ranged between (18-70) years and diagnosed with generalized or focal epilepsy. The study was done in Baghdad teaching hospital emergency room visitors and in epilepsy outpatient clinic of the same hospital during a periodof 9 months. All patients received Levetiracetam monotherapy (1000-3000) mg/day for at least 6 months. Vitamin D3 levels, calcium levels and ALP values were analyzed and patients were selected in our study according to the below criteria:

- Diagnosed cases of epilepsy on Levetiracetam (1000-3000 mg/day).
- Patient diagnosed with epilepsy and meet the ILAE criteria of diagnosis.
- Patients on Levetiracetam mono therapy at least for 6 months.

While Other Patients were Excluded According to the Following Criteria:

- Polytherapy patients on multi AEDs.
- Known epilepsy syndromes like LGS, Dravet or west syndrome.

Table 1: Mean Age and Epilepsy Duration Among Patients

Patient's variables	Mean	±SD
Age	35.06	13.3
Duration of epilepsy /years	5.188	3.685

Table 2: Mean Vit. D3, s. Calcium and ALP for our Patients

Investigations	Mean	±SD
Vit. D3 level ng/ml	22.3	9.863
Serum calcium mg/dl	9.094	0.7947
ALP (IU/L)	90.25	38.93

Table 3: Minimum and Maximum Levels of D3,S.Ca, ALP and Total Levetiracetam Doses

	Total dose Mg/day	Vit. D3 level ng/ml	S.calcium mg/dl	ALP (IU/L)
Number of values	32	32	32	32
Minimum	1000	9	7.6	14
Maximum	3000	42	10.3	174
Range	2000	33	2.7	160
Mean	1422	22.3	9.094	90.25
Std. Deviation	569.5	9.863	0.7947	38.93
Std. Error of Mean	100.7	1.744	0.1405	6.881

Table 4: Correlations Between Vitamin D3 Level and Total Daily Dose of Levetiracetam and Correlation of other Patient's Variables

Variables	Duration of epileps		Total dose MG/day		Vit d3 level ng/ml		S. calcium mg/dl		ALP (IU/L)		Age	
	r value	p value	r value	p value	r value	p value	r value	p value	r value	p value	r value	p value
Duration of epileps/years	1.00		-0.20	0.27	0.09	0.64	0.40	0.02	0.11	0.54	0.23	0.20
Total dose MG/day	-0.20	0.27	1.00		**-0.54**	**0.0013**	-0.29	0.10	-0.12	0.53	0.00	0.99
Vit d3 level ng/ml	0.09	0.64	**-0.54**	**0.0013**	1.00		0.49	0.00	0.15	0.40	-0.13	0.48
S. calcium mg/dl	0.40	0.02	-0.29	0.10	0.49	0.00	1.00		-0.11	0.56	0.10	0.57
ALP (IU/L)	0.11	0.54	-0.12	0.53	0.15	0.40	-0.11	0.56	1.00		-0.12	0.52
Age	0.23	0.20	0.00	0.99	-0.13	0.48	0.10	0.57	-0.12	0.52	1.00	

- Patients on Vitamin D3 supplementation or on unknown multivitamin supplement
- Patients having known bone disease, chronic liver or chronic kidney disease.

Statistical Analysis: Data were analysed using appropriate statistical methods with GraphPad prism. Continuous data were expressed as (mean±standard deviation (SD), while categorical data were expressed as percentages and frequincies. Correlation between variables was done by one way ANOVA and correlation matrix. A p-value of <0.05 was considered statistically significant. An r value means that variables negatively correlated when the value nearest to minus one and positively correlated when the value is nearest to one.

RESULTS AND DISCUSSIONS

The results revealed that the (mean±SD) of participants' age was (35.06±13.3) years and the (mean±SD) of epilepsy duration was (5.188±3.685) years as shown here in the (Table 1). The (mean±SD) of vitamin D3 level among patients was (22.3±9.863) ng/ml, with mean serum calcium level was (9.094±0.79) mg/dl and the (mean±SD) of ALP was (90.25±38.93) IU/L, as shown here in the (Table 2). The minimum level of vitamin D3 was 9 ng/ml and the maximum level was 42 ng/ml, while the minimum dose received by our patients was 1000 mg and the maximum was 3000 mg, as described in (Table 3). The correlation between vitamin D3 level and total daily dose of levetiracetam was negatively impacted with r value of-0.54 and with significant P value of 0.0013, other correlations between participants was not significant as demonstrated in (Table 4). The lowest level of vitamin D3 was with higher dose of levetiracetam as showed in (Fig. 1). This study analyzed the effects of levetiracetam as a mono therapy antiepileptic medication in patients with different types of epilepsy who showed that the mean epilepsy duration was(5.1±3.6) years and their mean age was (35.06±13.3) years. These results aligned with a study conducted by Marie-Christine Picot *et al* (2008) who reported that the (25-49) years age group has the highest prevalence of epilepsy and the percentage declined in the oldest group[16]. Our study showed that there were no significant effects of levetiracetam on serum calcium level nor on ALP level and this results were supported by many studies published previously like the study done by Meier E. Kraenzlin in 2011[17]. The present study showed that there was a negative correlation between levetiracetam and vitamin D3 level in patients taking levetiracetam as a mono

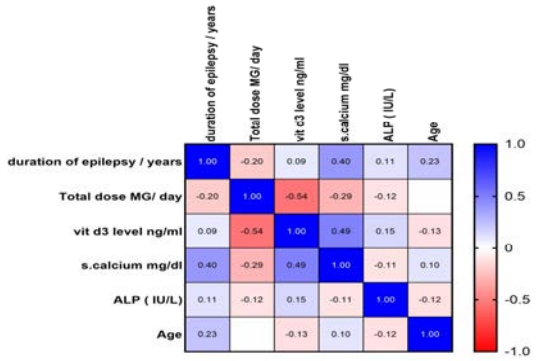

Fig. 1: The Pearson Correlation Between the Patient's Variables Investigated in this Study

therapy antiepileptic drug for at least 6 months with an r value of (-0.54) and it was a significant result as proven by the P value of 0.0013. This resultagreed with a study performed by Jafer Muhammad[18]. However, this study revealed that there were no significant correlations between levetiracetam and the serum calcium nor serum ALP levels. Nevertheless, the bone tissue is considered metabolically active and it is significantly influenced by the levels of active vitamin D3, serum calcium, parathyroid hormone levels and alkaline phosphatase. Since the active vitamin D3 level, may aid enhancing the absorption of calcium in the gastrointestinal system[19,20], therefore, increased percentage of inactive vitamin D metabolites versus active one will in turn result in a reduction of calcium absorption in gastrointestinal tract (GIT) system, with reduction of serum calcium However, in our study not clearly appeared may be because of the short duration of treatment and the limited sample size which is recommended for further research of Iraqi patients in the future to include larger sample size and longer duration of exposure to levetiracetam, in order to get more accurate and more reasonable results.

CONCLUSION

Our research reveals that patients receiving Levetiracetam as monotherapy for different types of epilepsy and for at least 6 months have significantly lower level of vitamin D3 and there was a negative correlation between them. At the same time, the study shows no significant correlation between Levetiracetam and serum calcium and AlP.

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