Comparison of 25-Hydroxy Vitamin D, Calcium and Alkaline Phosphatase Levels in Epileptic and Non-Epileptic Children.

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Abstract-

Objective: There is evidence for the existence of bone disease in epileptic patients. The goal of this study was the comparison of serum levels of calcium, alkaline phosphatase (ALKP) and 25-hydroxyvitamin D in ambulatory epileptic and non-epileptic children in order to evaluate the bone metabolism in epileptic patients.

Methods: In this prospective analytical study 48 ambulatory epileptic children who were treated by antiepileptic drugs for at least 6 months as case group compared with 48 children who were age and gender matched as control group. Patients with any neurological deficits and other systemic diseases were excluded. Data was collected by questionnaire and analyzed by spss software version 18.

Results: Mean of calcium level in case and control groups was 9.91 ± 0.675 and 10.08 ± 0.331 mg/dl respectively, means of ALKP in case and control groups were 703 and 607.75 IU/L respectively. Only difference between the ALKP were significant. Calcium levels, ALKP and vitamin D in any of the two groups were not associated with age and a sex but ALKP level in patients was higher and it was statistically significant. Calcium levels, ALKP and vitamin D in patients with drug type, dosage and duration of treatment were irrelevant.

Conclusion: The results of this study showed that calcium and vitamin D levels were in normal ranges in epileptic and control groups but ALKP levels were significantly higher in epileptic group which can be a valuable indicator of bone metabolism in these patients.

Key Words: epileptic children, vitamin D, calcium, alkaline phosphatase

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INTRODUCTION

It is estimated that over 50 million people all around the world suffer from epilepsy. Antiepileptic drugs remain the mainstay of treatment for epilepsy, on the other hand they are increasingly used in order to treatment the other situations such as migraine, psychiatric disorders and chronic pain, so their side effects on bone

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metabolism can be considered a serious health threat for many people especially for children[1]. There is evidence for the existence of bone disease in epileptic patients.The first evidence was found in the 1960's.In this study most patients were institutionalized and had suffered from obvious bone disease [2]. Recent studies that have focused on ambulatory patients, generally revealed more subtle abnormalities [3,4], but these findings do not decrease the importance of the subject. Additionally adult epileptic patients are in greater risk of bone fractures [5,6]. It is not only because of seizures but also it can be related to underling disease, gait disturbances and the effect of antiepileptic drugs on bone strength. There are some studies that have shown decreased bone mineral density in epileptic patients [7, 8]. Biochemical abnormalities of bone metabolism including hypocalcaemia, hypophosphatemia, vitamin D insufficiency and increased alkaline phosphatase have been reported in epileptic patients[9]. Childhood and puberty are the critical periods of bone mineralization. Identification of epileptic patients who have decreased bone strength and can be predisposed to bone fractures is an important issue in management of epilepsy. The goal of this study is the comparison of serum levels of calcium, alkaline phosphatase (ALKP) and 25-hydroxyvitamin D in ambulatory epileptic and non-epileptic children in order to evaluate the differences and possibility of using these factors for evaluating the bone metabolism in epileptic patients.

METHODS

This prospective analytical study was performed in Kermanshah University of Medical Sciences clinics in west of Iran. Forty eight ambulatory epileptic children aged 2 to 14 years who were treated with antiepileptic drugs as monotherapy for at least 6 months as case group enrolled in this study. Patients included were not receiving any other drugs (i.e. supplementary calcium or vitamin D) that might affect bone metabolism at least in previous month. All of the children had normal age- appropriate activity and consumed nutritionally adequate diets. Patients with any neurological deficits and other systemic diseases were excluded. None of the children had signs of rickets. Forty eight children who were age and gender matched to each of the patients selected as control group. Inclusion criteria for the controls were as follows: normal outdoor activity, no history of any type of seizure and the other diseases that might be treated by antiepileptic drugs, such as migraine and no previous history of any type of diseases that affect bone metabolism. None of them received supplementary calcium or vitamin D. After obtaining written consent from their parents, we collected detailed histories regarding demographic features, types and doses of antiepileptic drugs. Information of all patients was collected using a questionnaire. Venous blood samples were done for a hemogram and fasting was not required for tests. Serum calcium levels were measured by ARSENAZO technique and via auto analyzer device. Serum alkaline phosphatase was measured by DGKC method. Serum 25-hydroxyvitamin D level measurement was performed according to raidioimmune assay technique.

For an acceptable difference a power of study at 80%, confidence level 95% and a significant level of 0.05% was considered. Data were analyzed by using SPSS software version 16. Statistical analysis of data was done with Independent samples t test. For the two groups matched in terms of individual characteristics, drug type and duration of daily dose T-test (chi) or Fisher and Mann-Whitney were used.

RESULTS

Totally, 96 persons were studied. The age range of case group was 2-14 years with the mean of 7.1 ± 3.5 years. In the case group: Mean of calcium level was 9.91 ± 0.675 mg/dl, means of alkaline phosphatase703 ± 227.8 IU/L and mean of 25-hydroxyvitamin D was 26.52 ± 10.75 ng/ml. The age range in the control group was 2-13 years which its mean was 7.19 ± 3.6 years. Age was slightly higher in control group but it was not statistically significant. In this group the mean of calcium level was 10.08 ± 0.331mg/dl, mean of alkaline phosphatase was 607.75 ± 170.974 IU/L and mean of 25-hydroxyvitamin D was 30.09 ± 10.043 ng/ml. In comparison of two

Table 1. Description of Vitamin D levels base on gender in two groups

Groups	condition	Sever deficiency	deficiency	Insufficiency	sufficiency	Total
	Vitamin D level (ng/ml)	≤ 5	≤ 15	15-20	20 ≤	
Case (n=48)	male	0	0	5 (10.41%)	20 (41.6%)	N=25
	female	0	0	3 (6.25%)	20 (41.6%)	N=23
Control (n=48)	male	0	0	6 (12.5%)	21 (43.75%)	N=27
	female	0	0	9 (18.75%)	12 (25%)	N=21

Table 2. Means of drug types in case group

Drugs	Mean	Number of patients	Standard deviation
Phenobarbital	27.52	30	10.94
Carbamazepine	27.90	8	10.115
Sodium valproate	22.68	9	11.235
Topiramate	20.06	1	10.750

groups only difference between the alkaline phosphatase levels was significant and it was higher in patients' group. Calcium levels and 25-hydroxy vitamin D in each of the two groups were not associated with age and sex (Table 1). Alkaline phosphatase level was not associated to age in two groups (P.Value in control: 0.91 P.Value in case: 0.50) but in patients' group it was significantly higher in males. Calcium levels, alkaline phosphatase and 25-hydroxy vitamin D in patients were irrelevant with drug type, dosage and duration of treatment. Calcium levels, alkaline phosphatase and 25-hydroxy vitamin D in patients had no relation with duration of treatment and drug dosage, based on the drug type. Alkaline phosphatase in two groups based on age in range of 2-4 years had a statistically significant difference. Mean of drug duration based on the drug type showed no significant difference. (Table 2)

DISCUSSION

Calcium and vitamin D play important roles in bone metabolism and preserving adequate bone mass. In our study in case group the mean value of calcium was 9.91 ± 0.675 S.D. It was in normal limits and there was no significant difference between patients and control groups. This is in complete agreement with some other studies in which calcium levels had been in normal limits in epileptic patients [10-13], but it is in contrast to findings of some other studies that indicated hypocalcemia or significant lower levels of calcium in epileptic patients [14-16]. This difference can be related to studied population, in all of these studies the epileptic patients had mental retardation or cerebral palsy and had been institutionalized. The other reason can be the effect of monoteraphy; all of patients in our study had been treated with only one type of antiepileptic drug. Alkaline phosphatase as an important biochemical marker of bone metabolism is measured in epileptic patients. In our study mean of alkaline phosphatase level in patients' group was significantly higher than controls and also it was significantly higher in epileptic boys. There are many studies which revealed increasing level of alkaline phosphatase in epileptic patients [10,12,14-19], while the other study has not shown this finding [11]. Although in our study higher levels of alkaline phosphatase have been reported in patients who were treated with carbamazepine, but there was no statistical correlation between alkaline phosphatase levels and kind of

antiepileptic drugs. Duration of treatment was not significantly correlated with alkaline phosphatase levels. In this study mean of 25-hydroxyvitamin D in epileptic patients was 26.52 ± 10.75 ng/ml S.D. and in control group it was 30.09 ± 10.043ng/ml. Although it was lower in patients' group, but this difference was not significant. It is in complete agreement with results of some other studies [9-11, 20]. However; in some the other studies the levels of 25-hydroxyvitamin D have been lower in epileptic patients [14-16,21]. There was no correlation between 25-hydroxyvitamin D levels and duration of treatment, which has been showed in one other study [9]. We did not find any correlation between sex and 25-hydroxyvitamin D, while in at least one study, female sex was a significant risk factor for low vitamin D level [21], in their study, antiepileptic regimen was not a significant risk factor which is in line with our study. Significant controversy has been associated with definition of vitamin D sufficiency, insufficiency and deficiency. This is partly due to inadequate data to determine whether vitamin D below a specific threshold causes significant biochemical alteration and clinical manifestations. Sever vitamin D deficiency has been defined as 25-hydroxyvitamin D level of≤ 5 ng/ml [22]. According to studies, 25-hydroxyvitamin D level ≤ 15 ng/ml is indicative of vitamin D deficiency and its level ≥ 20 ng/ml is considered as vitamin D sufficiency, between 15 ng/ml and 20 ng/ml is defined as vitamin D insufficiency [23]. Considering these definitions, patients and controls in our study had not vitamin D defiecency. Monotherapy and normal physical activity are two possible reasons of these findings in our study. Enough sun exposure in this geographic area, in the west of Iran, can be the other possible explanation. In this area most days are sunny even in the fall and the winter. Interestingly, in one study, it has been recommended that 25-hydroxyvitamin D level should be maintain > 30 ng/ml and below this level parathyroid hormone levels begin to rise [24]. Even in the other study sufficient 25-hydroxyvitamin D is defined as levels more than 32 ng/ml [21].

The results of this study showed that mean calcium and vitamin D levels were in normal ranges in epileptic and control groups but alkaline phosphatase levels were significantly higher in epileptic group which can be a valuable indicator of bone metabolism in these patients. We emphasize that measuring calcium and vitamin D levels are essential in epileptic patients, especially when remember that they are in higher risk of falling and bone fractures.

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