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A PROSPECTIVE STUDY OF EFFECT OF ANTIEPILEPTIC DRUGS ON SERUM VITAMIN D LEVELS IN PEDIATRIC EPILEPTIC PATIENTS.

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ABSTRACT

Background: Antiepileptic drug (AED) induced disturbances of bone metabolism are usually accompanied by a fall in the 25(OH)D level, hypocalcaemia, secondary hyperparathyroidism, and increased bone turn over with a decrease in bone density.

Objectives: The objective of this study is to evaluate vitamin D status in epileptic children taking anticonvulsants.

Method: All newly diagnosed seizure patients aged between 1 months to 16 years with no co morbid condition, who had not received therapeutic vitamin D doses in last 6 months and whose vitamin D level were greater than 20 ngs/ml at the time of enrolment in the study were included in study.

Results: Out of 30 cases 13(43.3%) had decreased vitamin D levels to <20ng/dl where as in controls out of 30 only 4 (13.3%) had decreased vitamin D level to < 20ng/dl at the end of study.

Conclusions: This study identifies significant risk of vitamin D deficiency in ambulant children with epilepsy on antiepileptic drugs.

KEYWORDS : Antiepileptic drug, Bone density, hypocalcaemia, Vitamin D deficiency.

Introduction

Understanding the role of vitamin D in various health functions has increased exponentially 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 functioning, as well as glucose metabolism [1]. Antiepileptic drug (AED) induced disturbances of bone metabolism are usually accompanied by a fall in the 25(OH)D level, hypocalcemia, secondary hyperparathyroidism, and increased bone turn over with a decrease in bone density. In the pathogenesis of AED-induced bone disease, a central role is played by the pharmacokinetic interaction between AEDs and vitaminD:the enzyme, inducers carbamazepine, Phenobarbital, and pirmidone can activate pregnane X receptor which then upregulats expression of the 24-Hydroxylases, which can cause vitamin D defiency.[2] It is now assumed that vitamin D status is a major factor influencing life expectancy [3]. As regards the central nervous system vitamin D is involved in both brain development and adult brain function [4,5]. Deficient levels of vitamin D have been associated with several brain disorders including multiple sclerosis [6], Alzheimer [4,7,8] and Parkinson diseases [9], autism [10–12], schizophrenia [13], and cerebro vascular disorders [14]. Yet as compared, much less attention has been paid to epilepsy, the second major neurological disorder. Vitamin D is a member of a large family of steroid hormones signaling via nuclear and membrane associated receptors. It is synthesized from 7-dehydrocholesterol in the skin through exposure to ultraviolet B radiation. A number of vitamin D forms exist but vitamin D3 is the form naturally occurring in mammals. Metabolism of vitamin D3 is highly complex with the major route involving two consecutive hydroxylation steps taking place in the liver and the kidney. The first hydroxylation results in 25(OH)D, the major circulating form of vitamin D also used to measure vitamin D status. The second hydroxylation step is mediatedbythe1-alpha-hydroxylase enzyme and results in 1,25(OH)D. This is the active form of vitamin D meaning that this metabolite binds to the nuclear vitamin D receptor and mediates genomic responses. In fact, the 1-alpha-hydroxylase enzyme activity is not limited to the kidney but is present in various tissues throughout the body including the brain [11]. Vitamin D receptors as well as the 1-alpha-hydroxylase enzyme activity have been described in virtually all brain structures, neuronal and glial cell types [15]. The catabolizing enzyme of 1,25(OH)D which is upregulated at high levels of 1,25(OH)D is also present in the brain[16]. Based on its molecular structure, bioactivation in the nervous system and mechanism of action of vitamin D is considered as a neurosteroid [17,18]. Neurosteroids are increasingly recognized as modulators of neuronal excitability and seizure susceptibility [19]. Biochemical abnormalities of bone mineral metabolism in children receiving antiepileptic drugs, first identified in 1979 [20], is still a poorly studied topic from this region. In India, it is not a routine practice to supplement calcium or vitamin D in children on antiepileptic drugs; even in the UK, only 3% of Pediatric neurologists were reported to be using prophylactic calcium and vitamin D therapy for children on anticonvulsants [21]. Available evidence indicates that vitamin D levels in the Indian population are below the optimal levels recommended by the US Institute of Medicine or US Endocrinology Society [22].

The objective of this study was to evaluate vitamin D status in epileptic children taking anticonvulsants.

MATERIALS AND METHODS

This was a prospective case control study conducted over a period of two years in the department of paediatrics SKIMS Soura Srinagar. Proper clearance was taken from IEC before the beginning of study.

Participants, Case definitions:

All newly diagnosed seizure patients aged between 1 months to 16 years with no co morbid condition, who had not received therapeutic vitamin D doses in last 6 months and whose vitamin D level were greater than 20 ngs/ml at the time of enrolment in the study were defined as cases. For comparison purposes 30 age and sex matched patients who visited our OPD for minor complains like cough, loose stools formed our control group.

A thorough history, examination, relevant investigations were conducted which were entered in preformed proforma. Other information regarding the patient including age, sex, social status, developmental history, weight, height, signs of rickets, types of anti convulsant were entered in the Proforma.

Defining vitamin D deficiency

Vitamin D status was assessed by measurement of plasma 25(OH) vitamin D . Vitamin D status was defined as

- Vitamin D sufficient level of greater than 20 ng /ml.
- Vitamin D insufficient level between 10-20 ng/ml.
- Vitamin D deficient level less than 10 ng/ml.

25(OH)D3 levels were send in both cases and control before starting anticonvulsant therapy as well as after completion of 6 months of anticonvulsant therapy. THE serum 25(OH) vitamin D level was measured using chemiluminescence ELISA method in the department of Immunology and Molecular Medicine of our institute.

Analysis of data was done using SPSS18 for the categorical qualitative variables, frequency and percentage were calculated. Mean standard derivation (SD) was calculated from quantitative variables. Chi-square test was used to compare vitamin D levels among cases and controls and $p < 0.05$ was taken as statistically significant.

Results

A total of 3120 patients presented to our emergency department of these 251 were admitted for seizures, after applying exclusion criteria 221 were excluded from the study, remaining 30 formed the cases of our study**.** For comparison purposes 30 age and sex matched patients who visited our OPD for minor complains like cough, loose stools formed our control group.

There were no significant difference in demographic parameters of age sex and weight among cases and control group. **Table 1, Table 2 and Table 3**

Vitamin D (25-OHD) levels at the beginning of study:

The mean (SD) of serum 25-hydroxyvitamin D (25-OHD) levels was 49.57ng/dl(9.52) for cases and 52.63ng/dl(11.23) for controls. The difference was statistically insignificant as depicted by p-value of 0.259.**Table 4**

Vitamin D (25-OHD) levels at the end of study:

The mean (SD) of serum 25-hydroxyvitamin D (25-OHD) levels was 24.32ng/dl(8.75) for cases and 45.39ng/dl(9.83) for controls at the end of study. With p-value of <0.001 the difference of mean vitamin D levels is statistically significant. **Table 5**

Comparison of vitamin D reduction in cases and controls at the end of study:

13 (43.3%) patients of cases had decrease in vitamin D level to < 20ng/dl while in controls 4(13.3%) had decrease in vitamin D level to < 20ng/dl. Statistical analysis for data showed P-value of 0.021 that is statistically significant. **Table 6, fig 1**

Table 1: Age(years) distribution in cases and controls

Age (years)	N	Mean	SD	SEM	P-value
Cases	30	8.53	3.31	0.605	0.139
Controls	30	7.32	2.92	0.532	

Table 2: Gender distribution of cases and controls

Gender	Cases		Controls		P-value
	No.	%age	No.	%age	
Male	11	36.7	9	30.0	0.584
Female	19	63.3	21	70.0	
Total	30	100	30	100	

Table 3: Comparison of weight (kg) in cases and controls

Weight (kg)	N	Mean	SD	SEM	P-value
Cases	30	19.8	4.52	0.825	0.122
Controls	30	18.1	3.84	0.701	

Table 4: Comparison of mean vitamin D levels in cases and controls at the beginning of study

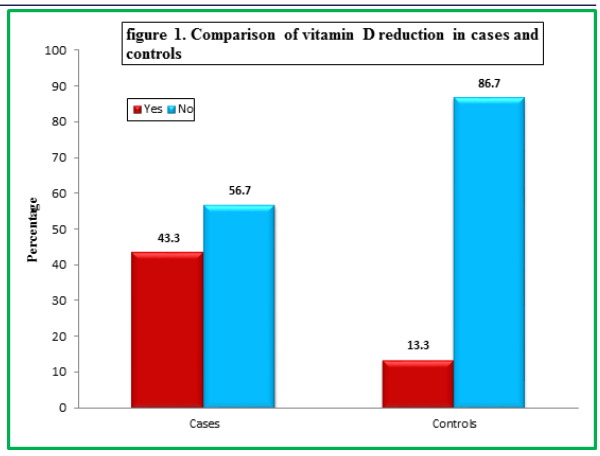
Vitamin D Levels	N	Mean	SD	SEM	P-value
Cases	30	49.57	9.52	1.738	0.259
Controls	30	52.63	11.23	2.050	

Table 5: Comparison of mean vitamin D levels in cases and controls at the end of study

Vitamin D Levels	N	Mean	SD	SEM	P-value
Cases	30	24.32	8.75	1.598	<0.001*
Controls	30	45.39	9.83	1.795	

Table 6: Comparison of vitamin D reduction in cases and controls

Vitamin D (< 20 ng/dl)	Cases		Controls		P-value
	No.	%age	No.	%age	
Yes	13	43.3	4	13.3	0.021*
No	17	56.7	26	86.7	
Total	30	100	30	100	



Discussion

Interaction between drugs and vitamin D have received on little or no attention in the medical and pharmaceutical world in the past, since more and more drugs are used for treatment of patients, this topic is increasingly relevant. Research has shown the adult epilepsy patients exhibit a deficiency of vitamin D.[23, 24] In pediatric patients, however controversies still remaining regarding the effect of anticonvulsants on vitamin D levels and bone heath.[25]

With recent estimates of 50 million people suffering from epilepsy globally, along with a rapid rise in the use of antiepileptic medication for other indications, the bone disease related to use of antiepileptic medications is emerging as a severe health risk for millions of people, particularly in childhood, which is the most critical period of bone growth.[26.]

In this study we intended to study the effect of anticonvulsant drugs on serum vitamin D levels. The present study revealed significant mean decrease in serum vitamin D levels in cases as compared to control group at the end of study. Out of 30 cases 13(43.3%) had decreased vitamin D levels to <20ng/dl where as in controls out of 30 only 4 (13.3%) had decreased vitamin D level to < 20ng/dl. Maryam R et al from Pakistan in 2015 in their study reported mean decrease in serum vitamin D levels in 32.4% cases and 5.9% controls. The larger number of cases with decreases in serum vitamin D levels in our study population can be explained by the fact of Kashmir being that state of India where winters are long and sunlight is scanty, so there is limited exposure to sunlight as people prefer to remain indoors during most of year.

This in the background of low intake of fortified vitamin D diet, can precipitate the hypovitaminosis D caused by AED.

In our study mean age of cases was 8.53± 3.31 years and in controls mean age was 7.32± 2.92 years it was similar to the study conducted by Fatma M et al were mean age for cases was 9.6±3.2 years and for controls it was 9.5±3.3 years and with study conducted by Maryam R et al where mean age of cases was 8.4±2.3 years and controls was 7.7±2.9 years .In our study female preponderance was more (63.3%) as compared to males (36.7%) it was in accordance with the study conducted by Fatma M et al where females percentage was more (56.6%) compared to males and in contradiction to the studies conducted by Ramya S etal and Maryam R et al where male cases were more 79% and 76% respectively . In the present study mean weight of cases was 19.8±4.5kg and mean weight of controls was 18.1±3.84 kg. There were no significant differences in age, gender and weight distribution.

Conclusion:-

This study identifies significant risk of vitamin D deficiency in ambulant children with epilepsy on drugs. Antiepileptics do affect the bone mineral metabolism adversely, as manifested by decreased vitamin D levels in serum of patients taking antiepileptic drugs. So there is need to monitor serum vitamin D levels and bone mineral density periodically during anticonvulsant therapy so that therapeutic Vitamin D and calcium supplementation should be started as early as possible

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