



A STUDY ON CALCIUM HOMEOSTASIS ABNORMALITIES IN PATIENTS TAKING CHRONIC ANTICONVULSANTS THERAPY

General Medicine

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ABSTRACT

INTRODUCTION: Epilepsy is one of the well-known disease entities causing significant morbidity. It is well recognized that chronic anticonvulsant drug therapy produces significant disorders of bone and mineral metabolism. Hence aim of our study is to evaluate the prevalence of calcium homeostasis abnormalities in patients on chronic anticonvulsant therapy, to assess the serum vitamin D level in patients on chronic anticonvulsant therapy and to study the relationship between the seizure control and hypocalcemia. **METHODOLOGY:** This was done as a cross sectional single centered prevalence study in a tertiary care teaching hospital, for a period of 6 months. In our study 100 patients with seizure disorder were randomly selected for the study, after applying the inclusion and exclusion criteria. Detailed history regarding epilepsy treatment, compliance and seizure control was taken from all the patients enrolled for the study. The data regarding the number and duration of anti-convulsant usage was collected. **RESULTS AND DISCUSSION:** Incidence of hypocalcemia and hypophosphatemia is related to duration and number of anticonvulsants, also in relation with ALP and PTH levels. Hence this study concludes that there is significant hypocalcemia and hypovitaminosis D in patients on chronic anti-convulsant therapy and we suggest that calcium and vitamin D supplementation may be beneficial.

KEYWORDS

Anticonvulsant, Vitamin D, PTH, Calcium.

INTRODUCTION

Epilepsy is one of the well-known disease entities causing significant morbidity. It is well recognized that chronic anticonvulsant drug therapy produces significant disorders of bone and mineral metabolism. In various anticonvulsant drug treated populations, the reported incidence of hypocalcemia, reduced serum 25-(OH) vitamin D concentration, elevated serum immunoreactive parathyroid hormone concentration, reduced bone mass varies from 40-60%.¹ Current evidence indicates that anticonvulsant drugs induced alterations in the hepatic metabolism of vitamin D or its biologically active metabolites, plays an important role in the pathogenesis of this disease. The reduced 25- hydroxy vitamin D concentrations observed in this disorder are attributed variously to increased hepatic microsomal catabolism of vitamin D and 25 hydroxy vitamin D or to a direct inhibition of hepatic conversion of vitamin D to 25 hydroxy vitamin D.

The laboratory abnormalities most commonly seen are hypocalcemia, hypocalciuria, reduced 25 hydroxy vitamin D as well as elevated alkaline phosphatase and immunoreactive parathyroid hormone in serum.² Hypocalcemia induced by anti convulsants, apart from causing bone abnormalities can also cause seizures per se. Hypocalcemic seizures are uncommon and under diagnosed complication of long-term therapy with AEDs. Loss of seizure control in a patient stabilized on AEDs is an indication to check the patient's calcium status. Proper treatment of this complication is vitamin D and calcium supplementation. Prophylactic supplementation with vitamin D is necessary in institutionalized patients treated with AEDs.

Hence, evaluation of these anti-convulsant induced complications assumes importance in view of their treatable nature, which forms the rationale of my taking up this study. Hence aim of our study is to evaluate the prevalence of calcium homeostasis abnormalities in patients on chronic anticonvulsant therapy, to assess the serum vitamin D level in patients on chronic anticonvulsant therapy and to study the relationship between the seizure control and hypocalcemia.

MATERIALS AND METHODS

This was done as a cross sectional single centered prevalence study in a tertiary care teaching hospital, for a period of 6 months in 100 patients. Ethical clearance was obtained before starting study and informed consent obtained from all patients. Patients attending the epilepsy clinic who are on the following single or multiple anti- convulsant commonly used in our hospital for a period of minimum 6 months were included in our study. Patients with chronic kidney disease, chronic liver disease, malabsorption syndromes, on other drugs influencing calcium hemostasis were excluded. The data regarding the number and duration of anti-convulsant usage was collected. The results were

analyzed using SPSS software.

RESULTS AND OBSERVATION

In our study 100 patients with seizure disorder were randomly selected for the study, after applying the inclusion and exclusion criteria. We stated with analyzing the prevalence of hypocalcemia in patients taking anticonvulsants for a long time (>6 months). In our study around 32 patients developed hypocalcemia with prevalence of 32%.

Table 1: Age distribution and hypocalcemia

Age Group in years		Normocalcemia	Hypocalcemia	Total	P value
Below 20	Number	20	10	30	>0.005
	percentage	66.7%	33.3%	100.0%	
21-30	Number	19	8	27	
	percentage	70.4%	29.6%	100.0%	
31-40	Number	21	12	33	
	percentage	63.6%	36.4%	100.0%	
Above 40	Number	8	2	10	
	percentage	80.0%	20.0%	100.0%	
Total	Number	68	32	100	
	percentage	68.0%	32.0%	100.0%	

In our study more patients were in 31-40 age group followed by less than 20 age group. The incidence of hypocalcemia was also similar in that age groups. There is no significant correlation between age and incidence of hypocalcemia in patients taking chronic anticonvulsant therapy. In our study male: female ratio was 1:1 with 50 male and 50 female patients. There is no significant association between the age distribution and incidence of hypocalcemia in patients on chronic anticonvulsant therapy as in our study 18 among male and 14 among female was having hypocalcemia.

In our study patients on single drug was 65 whereas 27 were on two drugs while rest had more than two drugs, Hypocalcemia was seen in 23 patients who had two or more drugs while only 9 had hypocalcemia in patients on single drug. This was statistically significant. Next we moved on to analyse relation of hypocalcemia with duration of drugs, in our study 52 were using drug for more than one year and 48 less than one year and among this 26 patients developed hypocalcemia, whereas only 6 developed hypocalcemia among those who were taking drug for less than a year. This was also statistically significant.

In our study, 23 patient had low vitamin D among which 21 had low calcium, whereas among 77 with normal vitamin D only 11 had low calcium. Presence of hypocalcemia was associated with low serum levels of vitamin D in a significant number of patients.

We further evaluated the PTH levels with hypocalcemia, where among 16 patients with elevated PTH all had hypocalcemia, whereas among 84 with normal PTH 16 had low calcium levels. Hence 50% of hypocalcemia patients had secondary hyperparathyroidism. Vitamin D levels were also correlated with PTH and 14 among 16 with elevated PTH had low Vitamin D, while 9 among 84 with normal PTH had low Vitamin D. Further we evaluated the relation between control of seizure and hypocalcemia, among 80 patients with good control 19 had hypocalcemia and among 20 with poor control 13 had hypocalcemia.

The prevalence of elevated alkaline phosphatase in patients taking anticonvulsants for a long time (>6 months) is 25%. There is no significant relation between age distribution of the study population and the incidence of elevated ALP. Similarly, no difference in incidence of elevated ALP was found between both the sexes. Similarly, we also analyzed the relationship between elevated ALP and number of anticonvulsants. Among 65 patients on one drug 10 had high ALP, among 27 with two drugs 10 had elevated ALP and among rest 8 with more than two drugs 5 had elevated ALP.

Next we moved on to analyze relation of high ALP with duration of drugs, in our study 52 were using drug for more than one year and 48 less than one year and among this 17 had high ALP, whereas only 6 had elevated ALP among those who were taking drug for less than a year. This was also statistically significant. Similar relation was also seen with calcium levels and ALP levels where high in patients with hypocalcemia which was also statistically significant.

We also correlated the serum phosphorus levels with various factors. To start with the frequency of hypophosphatemia increased with increase in number of anticonvulsants.

TABLE -2: Correlation of serum phosphorus and number of anticonvulsants

Number of drugs		Hypophosphatemia	Normal PO +4	Total	P Value
1	Number	9	56	65	<0.001
	Percentage	13.8%	86.2%	100%	
2	Number	16	11	27	
	Percentage	59.3%	40.7%	100%	
3	Number	6	2	8	
	Percentage	75%	25%	100%	
Total		31	69	100	

Similar more duration of drugs had direct correlation with low phosphorus levels. Also 87% of patients with low vitamin D level had low phosphorus levels which was statistically significant. Serum phosphorus level reduction was also had an direct correlation with high PTH level with 94 percent of patient with high PTH levels has hypophosphatemia.

DISCUSSION

The aim of the thesis was to study the prevalence of hypocalcemia among patients on chronic anti-convulsant therapy. The prevalence of hypocalcemia among our study population was 32%. In a study done previously by Schmitt BP et al¹ on 56 patients taking chronic anti convulsants, 29% were found to have hypocalcemia.⁴ The correlation between the number of anti-convulsant drugs the patient taking and the presence of hypocalcemia was statistically analyzed. Among the patients on single drug therapy, the prevalence was 28.1%. Patients taking two drugs had a prevalence of 53.1% and for those on three drugs the value was 75%. Hence the number of anti-convulsant drug usage correlated directly with the chance for hypocalcemia and the differences were statistically very significant ($p < 0.001$).

The duration of anti-convulsant usage and whether that had a significant effect on the prevalence of hypocalcemia was analyzed. Those taking drugs less than 12 months had a prevalence of 11.5%, while, of the patients taking drugs for more than 12 months, 81.3% had hypocalcemia. The difference when analyzed statistically, was significant, with a p value < 0.001 .

The serum levels of vitamin D was measured in all these patients and we found that, out of the 32 patients with hypocalcemia, 30 (93.8%) also had low levels of vitamin D. But in the normocalcemic group hypovitaminosis D was present only in 14.3% with the difference in prevalence being statistically significant ($P < 0.001$). In a similar study done on 56 patients taking chronic anti convulsants, Theodore J. Hahn

et al reported that the serum calcium concentration of the patients correlated with serum vitamin D levels.⁵

Next the presence of low vitamin D levels in hypocalcemic patients was studied, and it was found that among the 23 patients of hypovitaminosis D, 21 (91.3%) patients also had hypocalcemia and the finding was statistically significant. The relationship between control of seizures and the presence of hypocalcemia was studied. It was found that, in patients with hypocalcemia, seizures control was poor, than in those with normocalcemia, with a P value of the difference being < 0.001 . A similar finding was reported in the study done by Ali FE et al.⁶ In this study, in addition to calcium levels, we also studied the correlation of serum Alkaline phosphatase levels with anti-convulsant drug usage. Elevated Alkaline phosphatase levels was found in 25 of the 100 patients studied. Of these patients 19 also had hypocalcemia (76%) while the remaining 6 (24%) had isolated elevation of Alkaline phosphatase. In the study done by Schmitt BP et al, quoted previously, a similar finding was reported, with elevated ALP levels in 27% of the study group.⁴

The elevated Alkaline phosphatase levels were analyzed with respect to the number of drug usage. With single drug use, the prevalence was 15.4% while with two and three drugs usage, the prevalences were 37% and 62.5% respectively. Thus more the number of drugs used, more the chances of elevated Alkaline phosphatase levels. Also the effect of duration of therapy on alkaline phosphatase levels was considered. Patients on drugs for less than 12 months had a prevalence of 15.4% while those taking drugs for more than 12 months had a greater prevalence of 35.4%. All the above mentioned findings were significant on statistical analysis ($p < 0.001$).

The coincidence of occurrence of hypocalcemia and elevated ALP were analyzed. Of the 32 patients with hypocalcemia, 19(59.3%) also had elevated ALP. Isolated elevation of ALP alone was found in 6 (8.8%) patients. The prevalence of elevated parathyroid hormone in patients with hypocalcemia was analyzed and was found to be present in half such patients, with statistical significance. Also, the correlation between low vitamin D and PTH levels was analyzed and it was found that, of the 23 patients with low vitamin D, 14 had elevated PTH levels, the number being significant on analysis with p value being < 0.01 . Serum phosphate levels were done for the patients and it was found that hypophosphatemia was associated with either a greater number of, or longer duration of anti-convulsant treatment and also with hypovitaminosis D and elevated parathormone levels. The associations were found to be statistically significant with $p < 0.001$.

CONCLUSION

There is a significant prevalence of hypocalcemia in patients on chronic anticonvulsant therapy. The number of anti-convulsant used, as well as the duration of usage have a significant correlation with the prevalence of hypocalcemia. Hypocalcemia in patients has a significant association with poor seizure control, when compared with normocalcemic patients. Elevated Alkaline phosphatase levels were found in patients on chronic anti-convulsant therapy either in isolation or in combination with hypocalcemia. Elevated Alkaline phosphatase levels correlated significantly with the duration and number of anti-convulsant drug usage. Hence this study concludes that there is significant hypocalcemia and hypovitaminosis D in patients on chronic anti-convulsant therapy and we suggest that calcium and vitamin D supplementation may be beneficial.

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