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'TOO EXCESS IS BAD'- VITAMIN D TOXICITY IN ADULT

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Abstract: Vitamin D deficiency is increasingly detected now days, making clinicians prescribe Vitamin D in oral or inject able preparation to patients. In developing countries like India where there is enormous patient load & cost constraints regular Vitamin D monitoring is not routinely done. The case in light of current indiscriminate un monitored Vitamin D use reinforces the importance of monitored treatment to prevent toxicity. The case also emphasis the importance meticulous history taking, the art that is loosing its shine in the era of modern medicine where there is total reliance on investigational techniques for medical diagnosis. The case of elderly male been administered Vitamin D over long period and subsequently manifesting as toxicity. The diagnosis relied on Vitamin D intake history which went unnoticed making clinical diagnosis difficult. The art of clinical history taking plays a pivot role in diagnosis and is of prime importance as emphasized in the case.

Keywords: Clinical History , Vitamin D toxicity.

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INTRODUCTION

Vitamin D is an important pro-hormone which, besides playing important roles in calcium homeostasis and bone mineral metabolism, is now recognized to subserve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth as well as immune modulation.[1] The daily requirement of vitamin D is about 200-600 units.[2] Fortification of foods with vitamin D is done to correct environmental deficit(less ultraviolet exposure),but it does not corrects nutritional deficit. Vitamin D deficiency leads to rickets in children and osteomalacia in adults. Vitamin D deficiency is widely prevalent across the globe.[3,4]

Vitamin D deficiency is defined as serum 25 (OH)D of less than 20 ng/ml and Vitamin D insufficiency as levels between 21-29 ng/ ml, respectively. [3,4]

Recently voluminous data has emerged on association of vitamin D deficiency with many chronic diseases. The antiproliferative, prodifferentiative, and immunomodulatory actions of vitamin D are being investigated for the potential treatment of many pathologic conditions including psoriasis, type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, hypertension, CAD, and many cancers. This has lead to widespread use of vitamin D supplements in populations. Increased use of vitamin D formulations and use of higher doses has lead to an increased incidence of vitamin D toxicity. According to the American Academy of Pediatrics, serum vitamin D levels above 250 nmol/L (100 ng/ml) are considered as hypervitaminosis D, whereas serum levels above 375 nmol/L (150 ng/ml) are associated with Vitamin D intoxication.[6,7]

As such clinicians frequently treat patients with vitamin[4,5] D for diverse clinical symptoms and these doses may at times be inappropriately high.

We present our experience of vitamin D toxicity in a 87 year old man who had received high doses of vitamin D and presented with features of vitamin D overdose.

CASE REPORT

An 87-year-old male was admitted to our hospital with a history of weakness, altered sensorium, pain abdomen since a month. He had been diabetic and hypertensive for past ten years. There was no history of chest pain, fever, cough and headache. On physical examination, there was presence of pallor with the absence of icterus and edema .The patient was in altered sensorium. There was no abnormality on chest X-ray and cardiovascular examination was normal. The patient vitals were: blood pressure 128/82mmHg, pulse 72/minute, respiratory rate 20/minute, and temperature 37.6°C.

An examination of his central nervous system showed generalized muscle weakness without any focal neurological deficit. His deep tendon reflexes were reduced. An old MRI brain revealed small infarcts with ischemic demyelination along with bilateral periventricular deep subacute white patches with normal pressure hydrocephaluis as lateral ventricle was disproportionately prominent. CT chest & ultrasonography of neck was normal. USG abdomen showed diverticulae at second part of duodenum, right sided inguinal hernia and moderate degree of prostate hyperplasia .The X- ray of KUB region showed bilateral hyperdense medulla- Medullary nephrocalcinosis. There was calculus at interpole calyx of left kidney. On laboratory investigation the following results were obtained: hemoglobin 8.8g/dL, Red blood cell count- 4.13 x 10^9 / mm^3, White blood cell count 9.5×10^3/mm^3, platelet count 408×10^9

Polymorphs- 82%, Lymphocytes- 15%, Eosinophils- 1% & Monocytes-2%. Serum Sodium levels- 131mEq/L, Serum Potassium 4.9mEq/L, Alkaline phosphatase 97 U/L, and Erythrocyte sedimentation rate 76mm. Serum ACE levels were 38.4 ug/L, HbA1c-5.8%, PSA- 4.22 ng/ml, Alkaline Phosphatase- 97 IU/L, Serum Iron-56.64 ug/dl, TIBC 248 ug/dl, Transferrin – 22.83 mg/dl, , Ferritin- 925.39 ng/ml, TSH- 1.62 mcIU/ml, T3- 1.23 ng/ml , T4- 6.42 mcg/dl . Blood urea- 24mg/dl and creatinine-1.5 mg/dl .HIV, HBsAg and HCV profile were non-reactive. Lumbar puncture &bone marrow examination were unremarkable. Serum protein electrophoresis was suggestive of Polyclonal gammopathy with urine been negative for Bence Jone proteins.

The patient was earlier hospitalized in other hospitals for complaints of altered sensorium but a month long work up did not point any significant biochemical or radiological finding that could explain altered sensorium. The case on admission to our hospital was referred to pathology advisory service. Upon review of previous investigations and reports a detailed work up was done. Elaborate patient history was again taken by pathologist. As the patient was unable to give history, it was taken from his attending son who revealed that the patient had long standing bilateral knee pain and was given Vitamin D as inject able and later oral doses weekly over a period of 15-18 months on the advice of family medical practitioner. Immediately Serum & urinary Calcium levels along with Vitamin D level were done. Serum Calcium was 12.7 meq/L, urinary calcium was 5418 mg/dl and Vitamin D level was 425 nmol/L. A serum parathormone assay was advised by the pathologist it came out to be extremely low less than 0.23 IU/ml. Normal renal function tests with absence of M band on electrophoresis with absence of Bence Jone proteins ruled out Chronic Kidney disease and Multiple Myeloma. Possibility of Vitamin D toxicity was suspected as other causes were ruled out along with history of above normal doses of Vitamin D.

He was treated with intravenous fluid therapy and diuretics with regular monitoring of serum calcium and creatinine levels. The earliest sign of improvement was seen after 48 hours in the form of improved sensorium. Meanwhile patient's Vitamin D level was done which came out to

be 190ng/ml . The therapy was continued for fifteen days so that calcium levels returned to normal range .He was discharged with a prescription of an antihypertensive and calcium-restricted diet along with good hydration.

DISCUSSION

There is wide gap between therapeutic and toxic doses, [8,9,10] of Vitamin D which makes the likelihood of toxicity uncommon in clinical practice. At the same time the frequent indiscriminate, unmonitored use of vitamin D supplements (oral or intravenous) put patients at increased risk of toxicity. There are sporadic reports of vitamin D toxicity reported in literature.[10,11]It is a condition where an increase in the 25-hydroxyvitamin D (25OHD) levels is associated with either hypercalcemia or hypercalciuria, or both.[7]Hypervitaminosis Vitamin D intoxication can manifest as any of the symptoms like Nausea, Vomiting, anorexia, abdominal pain, constipation, growth retardation, peptic ulcer, Polydipsia, Polyuria, dehydration, hematuria, hypernatremia, hypokalemia, nephrolithiasis, distal renal tubular sclerosis, Acute & Chronic renal failure, hypotonia, reduced deep tendon reflexes, confusion, seizures, lethargy, coma, psychiatric manifestations, arrhythmias, accumulation of calcium in myofibers, ST elevation, cardiomyopathy, bone pain, muscle weakness, osteopetrosis, conjuctival calcification, band keratopathy, itching & metastatic calcification. The mechanism of vitamin D toxicity in hypervitaminosis D is postulated to be an overwhelming [7,12] response of the vitamin D signal transduction process, whereby the catabolic system involving the CYP24A1 is unable to keep up with the target cell levels of activated vitamin D metabolites.[9]

Three major theories have been put forth by researchers about the mechanisms of vitamin D toxicity. All involve increased concentrations of a vitamin D metabolite reaching the vitamin D receptor in the nucleus of target cells and causing exaggerated gene expression.[9,12]

1. Vitamin D intake raises plasma 1 alpha-25$(OH)_2$ D concentrations which increase cellular 1-2. Alpha 25 $(OH)_2$ D concentration.

2. Vitamin D intake raises plasma 25(OH)D to concentrations that exceed the vitamin D binding protein, binding capacity and "free 25(OH)D" enters the cell, where it has direct effects on gene expression.

3. Vitamin D intake raises the concentrations of many vitamin D metabolites, especially vitamin D itself and 25(OH)D. These concentrations exceed the DBP binding capacity and cause release of "free" 1-alpha 25$(OH)_2$ D, which enters target cells.

Of the three hypotheses put forward to explain the triggering event of toxicity, increases in total 25(OH)D and free 1 alpha-25(OH) unproven. [9,12]The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life approximately 2 months), whereas its main transported metabolite, 25 hydroxy vitamin D (3) (25(OH) D(3), has a half-life of approximately 15 days. However, even in the absence of definitive evidence to establish the responsible metabolite, the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D good biomarker for toxicity.[9,12]

Even though vitamin D toxicity is extremely rare, due to the wide therapeutic index, it does occur at excessively high doses.[13] The guidelines of the Food and Nutrition Board of the USA specify 2000IU as the highest vitamin D intake that healthy adults can consume 3is a daily without risk of hypercalcemia.[13,14]

There are few lessons to be learnt from the present case. Firstly, unmonitored Vitamin D administration without any documentation of Vitamin D deficiency should be discouraged as it increases risk of toxicity. Second and more importantly meticulous clinical history of patient is indispensible to clinch diagnosis. In the present case, the patient although was admitted for a month for the same complaints but diagnosis could not be made. The patient was subjected to investigations, procedures without successful outcome as the basic of clinical history taking was not followed stringently. The history of Vitamin D intake over long period was core stone for diagnosis but unfortunately it was missed and diagnosis delayed.

CONCLUSION

Due to wide therapeutic index and lack of monitoring, many cases of mild vitamin D toxicity go unnoticed, only the cases with serious side effects attend hospitals, thus reducing the actual number of cases of hypervitaminosis D.[10] But inspite of that fact, still hyperviatminosis D is not so common but recommending vitamin D and calcium to patients without any laboratory evidence of vitamin D deficiency is not warranted and one should strictly have the documented deficiency before they are prescribed vitamin D supplements to prevent them from serious side effects of vitamin D overdose.

The art of clinical history taking plays a pivot role in diagnosis and is of prime importance as emphasized in the case.

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