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Case Report :

Acute Vitamin D toxicity- without hypercalcemia

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Abstract:

Recommendation and concern over vitamin D deficiency has led to widespread use of vitamin D supplements, containing up to 60,000 IU/unit dose (400 IU=10μg) in practice from infantile age. Vitamin toxicity also has increased proportionately. Vitamin D toxicity usually occurs over a time period and presents with hypercalcaemia. Infants are particularly vulnerable to toxicity associated with vitamin D overdose. However, It is rare to find cases of vitamin D intoxication that present with dramatic life-threatening symptoms in children. We present the unique case of acute vitamin D toxicity without hypercalcemia where malnourished child was given vitamin D supplement of higher concentration and presented within two days with signs of lethargy and hypotonia. Vitamin D levels were found to be high and came to normal after four week.

Keywods: Hypervitaminosis D; Vitamin D; Vitamin D associated toxicity

Introduction: Vitamin D is one of four fat-soluble vitamins. With parathyroid hormone, it regulates calcium homeostasis tightly. When the serum calcium level is low, calcitriol, the biologically active form of vitamin D, restores homeostasis through increased dietary calcium absorption through the gut and through increased bone resorption. Guidelines issued by the AAP and the National Academy of Sciences indicate that all breastfeeding infants and non breastfeeding infants who drink <500 ml (<16 oz) of vitamin D-fortified formula or milk per day should receive 400 IU of vitamin D per day.[1, 2, 3] Studies done in India also point towards significant vitamin D deficiency in all age group. [4]

Unintentional vitamin D poisoning has been associated with over fortification of milk, adulteration of table sugar, contamination of cooking oil and with use of an over-the-counter supplement by an adult.[5,6,7,8] Vitamin D has a median lethal dose of 21 mg/kg and, in overdose, affects all major organ systems. 9 The symptoms of vitamin D toxicity stem from the deposition of calcium phosphate crystals in soft tissues throughout the body, which can occur once the calcium-phosphate product is >60 mg/dl. Early symptoms of hypercalcemia include anorexia, nausea, vomiting, weakness, lethargy, constipation, and nonspecific aches and pains. Renal function can become impaired as a result of nephrocalcinosis. Vascular calcification leads to renal hypertension. Because vitamin D is lipophilic and is stored in fat tissues, the effects of vitamin D toxicity can persist ≥2 months after exogenous source is removed Treatment for vitamin D toxicity includes immediate removal of the exogenous source, intravenous fluid hydration, loop diuretics (Thiazides promote calcium retention), glucocorticoids, and a low-calcium diet. Glucocorticoids decrease the production of 1, 25-dihydroxyvitamin D3, which decreases dietary absorption of calcium. It also prevents calcium from being resorbed in renal tubules, thereby promoting the urinary excretion of calcium.[10,11]

Exogenous calcitonin can also be used. The associated risks, specifically the risk of allergic reactions, have decreased because it no longer is derived from salmon but now is available as recombinant human calcitonin.[12] It inhibits bone resorption and blocks release of calcium and

phosphate into the serum. The use of bisphosphonates, such as pamidronate, is accepted widely for adults, but uses in children have been only anecdotal and thus the safety is unknown. Hemodialysis can be used to treat hypercalcemia and can lower serum calcium levels rapidly. Because rebound hypercalcemia is predictable after vitamin D intoxication, hemodialysis should be reserved for life-threatening, medically unmanageable indications, such as acute or chronic renal failure and hypercalcemic crisis. [13]

Recent studies in infants raise a potential need for monitoring vitamin D levels when doses at or above the currently recommended upper range are used. Further studies are needed to clarify these findings.[14,15,16] The Drugs and Therapeutics Committee of the Pediatric Endocrine Society suggests obtaining serum 25-hydroxyvitamin D levels in infants and children who receive long-term vitamin D supplementation at or above the upper level intake that is currently recommended.2 Because vitamin D is used so readily, it is important to understand how dosing errors can lead to overdoses with potentially life-threatening consequences.[10]

Case Report:

A twenty month old female toddler, weighing 8.1with height 0f 77 cm came to OPD with complains of not thriving well in spite good appetite. Her weight and height were in between first and third percentile and her weight for height was just above third percentile. She did not have signs of severe acute malnutrition. Her motor and mental development was age appropriate. Vital signs were normal and general examination revealed mild chest beading and protuberant abdomen. Her dentition was normal. Systemic examination did not reveal any abnormality. She was diagnosed clinically as moderate acute malnutrition and X-ray of wrist with elbow was advised for signs of possible rickets and bone age. X-ray findings were not suggestive of radiological rickets. Blood tests were not done, as parents were unwilling. Child was prescribed vitamin D sachets containing 60000 units once a day for five days along with syrup of Calcium.

After two days child was brought for decreased appetite and lethargy. Blood Glucose by finger prick method was normal. Parents were advised admission, but refused saying they would observe at home. They were counseled to give sugar rich liquids and food. Next day, child again came for admission as she was more lethargic and was unable to stand and walk. On examination, she was responding to name and did not have focal neurological signs. The deep tendon reflexes however were depressed. There were no meningeal signs.

Laboratory testing showed a serum Ca2+ concentration of 9.4 mg/dL (normal: 8.4–10.2 mg/dL). Complete blood count and electrolyte concentrations were within normal limits, as follows: Na+, 139 mEq/L; K+, 3.7 mEq/L; Cl−, 102 mEq/L; CO2, 28 mEq/L; blood urea nitrogen, 13 mg/dL; creatinine, 0.5 mg/dL; glucose, 107 mg/dL; Mg2+, 1.3 mg/Dl, CPK levels were. Urine routine examination was normal and no calcium crystals were found. An electrocardiogram showed normal sinus rhythm, with a regular rate and normal intervals.

Parents were not willing for CSF study. Child was started on fluids; a report AFP surveillance team was done. All oral medications were stopped and child was observed for progression or improvement. Next day, child was not showing clinical improvement except improvement in consciousness, possibility of uncommon causes were searched for. Acute Vitamin D intoxication was thought as this was one of the two medicines children has consumed recently. Surprizingly, Vitamin D levels were very high i.e. 151 ng/ml. (Normal: 10–68 ng/mL).

After forty eight hours, Child started standing and walked with support. Child started walking and running normally in next forty eight hours. Two specimens of stool were collected for polio studies by authorities. Baby was discharged without any medication and asked to follow every weekly. After one month, only S. Vitamin D levels were done

which were 21ng/ml.Child was symptomatically normal throughout this period. Meanwhile AFP report of polio was negative.

Discussion:

There are many cases of acute Vitamin D intoxication in literature searched. All the cases as discussed in introduction were associated with hypercalcaemia and high Vitamin D levels. Our case is unique in a way that it is purely associated with high Vitamin D level and signs of intoxication with normal metabolic parameters. We were able to show that vitamin D levels also came to normal levels after reasonable time.

Fermin Barrueto, Jr,et al. have presented the unique case of a previously healthy, 2-year-old boy with resistant hypercalcemia and hypertension resulting from an unintentional overdose with an imported vitamin D supplement. The patient presented initially to the emergency department with colic and constipation and was discharged after a benign physical examination. The symptoms persisted and, on the second visit, the patient was found to have a serum calcium level of 14.4 mg/dL. Despite therapy with intravenously administered 5% dextrose solution at one-half normal strength, furosemide, calcitonin, and hydrocortisone, the calcium concentration increased to 15.0 mg/dL on the second hospital day and did not decrease until the fourth hospital day, when it fell to 13.9 mg/dL. The vitamin D concentration peaked at 470 ng/mL on hospital day 3. With additional questioning, the mother revealed that she had been giving her son a daily dose of 1 ampule of Raquiferol, an imported vitamin D supplement, instead of the recommended 2 drops per day. Each ampoule contained 600000 IU of vitamin D; therefore, the boy received a total of 2400000 IU over 4 days. The patient's hypercalcemia persisted for 14 days and was complicated by persistent hypertension. No renal, cardiac, or neurologic complications were noted. At discharge, the vitamin D concentration was still elevated at 389 ng/mL and the total calcium level had decreased to 11 mg/dL. The boy made a complete clinical recovery. This case highlights the need for caution when using imported and/or unregulated medicines, as well as the dangers of parental dosing errors. [14]

Ketha et al report a case of vitamin D3 associated toxicity in a 4-month-old female who was exclusively breast-fed and received an oral liquid vitamin D3 supplement at a dose significantly higher than recommended on the label. The vitamin D3 content of the supplement was threefold higher (6000 IU of D/drop) than listed on the label (2000 IU). Due to overdosing and higher vitamin D3 content, the infant received ~50,000 IU/day for two months resulting in severe hypercalcaemia, hypercalciuria and nephrocalcinosis. [15]

Özkan B, Hatun Ş, Bereket A. reviewed and commented that Vitamin D intoxication has been reported more frequently in recent years. This may be attributable to an increase in vitamin D supplement intake due to an understanding of the role of vitamin D (25OHD) in the pathogenesis of several diseases. The symptoms and findings associated with VDI are closely related to serum calcium concentration and duration of hypercalcemia. In patients with VDI, hypercalcemia, normal or high serum phosphorus levels, normal or low levels of alkaline phosphatase (ALP), high levels of serum 25OHD, low serum parathyroid hormone (PTH), and high urine calcium/creatinine are usually present. Serum 25OHD levels above 150ng/ml are considered as VDI. In conclusion, the diagnosis of vitamin D deficiency rickets (VDDR) without checking serum 25OHD level may cause redundant treatment that leads to VDI. All patients who are clinically suspected of VDDR should be checked for serum vitamin D status and questioned for previous vitamin D administration before starting vitamin D therapy. On the other hand, parents of all infants should be asked whether they are using dietary or oral supplements, and serial questioning may be required during supplementation to avoid excessive intake.[16]

Vitamin D supplements used for the treatment of rickets are too concentrated for use as a routine supplement. Although it is not necessary to educate all parents about the symptoms of acute vitamin D intoxication, in appropriate situations they should

be informed about the possible dangers of vitamin D and the importance of careful dosing.[17] Stross regimen followed since long advocates vitamin D megadose of 3-6 lakh for treatment of rickets. Hema Mittal et al. in a randomized controlled trial of treatment of rickets with 300000 and 600000 units of vitamin D demonstrated that even a dose of 600,000IU may not be enough to normalize serum 25(OH) D(beyond 20 ng/mL), in Indian children with rickets. They advised daily vitamin D supplementation for all children for 12 weeks, after completing the study duration of 3 months. They were not sure, whether to start with routine daily vitamin D supplementation, immediately following the mega dose. This approach would have needed a strict monitoring for vitamin D intoxication. They concluded that a therapeutic oral dose of 300,000 IU of vitamin D can be safely substituted for 600,000 IU for treating nutritional rickets in under-five children. None of the two regimes is effective in normalization of vitamin D status in majority of patients, 3 months after administering the therapeutic dose. Studies are needed to document the optimal strategy of vitamin D3 supplementation in children treated with mega-dose of vitamin D, for replenishing the body stores. [18]

Researchers[13] have proposed 3 major theories about the mechanism of vitamin D toxicity. All involve increased concentrations of a vitamin D metabolite reaching the VDR in the nucleus of target cells and causing exaggerated gene expression. At issue is the offending vitamin D metabolite and how it becomes elevated. The 3 hypotheses to explain this are as follows:

1. Vitamin D intake raises plasma 1α, 25(OH)2 D concentrations, which increase cellular 1α,25(OH)2D concentrations.
2. Vitamin D intake raises plasma 25(OH) D to μmol/L concentrations that exceed the DBP 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" 1α, 25(OH) 2D which enters target cells.

Our current understanding of the components of the vitamin D signal transduction machinery (DBP, activating CYPs, VDR, and CYP24) allows us to theorize in broad terms about how vitamin D toxicity might arise from hypervitaminosis D. Of the 3 hypotheses put forward to explain the triggering event for toxicity, increases in total 25(OH) D and free 1α, 25(OH)2D concentrations are the most plausible, although they remain unproven. 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) D3 is a good biomarker for toxicity, and the threshold for toxic symptoms is ≈750 nmol/L. This threshold value implies that 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nmol/L, are safe and still leave a broad margin for error because values significantly higher than this value have never been associated with toxicity.

Our case is probably the first case reported with high vitamin D levels in blood following ingestion of high dose of vitamin D and presenting with acute toxicity symptoms mainly lethargy and weakness without hypercalcaemia. We were able to show that indeed at end of one month child was asymptomatic and her vitamin D levels had come down to lowest level of normal. This suggests that the symptoms and signs were likely to be due to acute Vitamin D toxicity. Unfortunately, we were unable to do all these investigation due various reasons including patient's unwillingness. We have not done parathyroid hormone levels and urine calcium /creatinine ratio in our case. This may be a lacuna in otherwise straight forward rare case. But since, this child did not have hypercalcaemia; the question of urinary calcium did not arise. This mechanism has possibly genetics and mutational basis. It is possible that measurements of parathyroid hormone (PTH) and vitamin D

metabolites 25(OH) D3, 1,25(OH)2D3, 3-epi-25(OH)D3 and 24,25(OH)2D3 are useful to investigate whether the underlying cause of vitamin D toxicity is due to direct action of Vitamin D or due to probable genetic abnormality in metabolism of Vitamin D in our patient.

Conclusion:

Our case is unusual because a malnourished child after receiving 1,20,000 units of vitamin D has developed acute and dramatic presentation of toxicity. After ruling out common causes of lethargy; ONLY vitamin D levels were very high without hypercalcaemia. We were able to show after one month that vitamin D levels came down to lower limits of normal and child was asymptomatic. This proves our hypothesis that the symptoms were due to vitamin D alone.

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