EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 7
340-343
Year: 2019

HYPERVITAMINOSIS D: A RARE PEDIATRIC CASE REPORT

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Article Received on 14/05/2019 **Article Revised on 04/06/2019** **Article Accepted on 25/06/2019**

ABSTRACT
Vitamin D toxicity (VDT), also called hypervitaminosis D, is a rare but potentially serious condition that occurs when there is excessive amount of vitamin D in the body. Vitamin D deficiency is highly prevalent in India. This has set off a trend among medical practitioners to prescribe vitamin D supplements empirically. Whilst this approach is generally safe, but in predisposed individuals it may lead to hypervitaminosis D. Although VDT is rare, the adverse effects can be life threatening if not promptly identified and treated. To establish a diagnosis of hypervitaminosis D there has to be a clinical and biochemical hypercalcemia along with calciuria and hypoparathyroidism with elevated serum vitamin D levels. Here we report a rare paediatric case of acute toxicity due to excessive vitamin D supplementation. He required steroid therapy and responded well to treatment with reversal of symptoms. Our report highlights the need to use vitamin D therapy judiciously and to remain vigilant for side-effects.

KEYWORDS: Hypervitaminosis D, hypercalcemia, hypoparathyroidism.

INTRODUCTION
Vitamin D is an important pro-hormone which plays an important role in calcium homeostasis and bone mineral metabolism, and 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] Because of wide therapeutic index, vitamin D toxicity is extremely rare, but does occur at excessively high doses. Vitamin D intoxication can be iatrogenic, due to self-medication or accidental with over fortification of milk or contamination of common dietary constituents like table sugar or cooking oil.[2],[3] Because of the growing awareness of vitamin D deficiency and related health problems, vitamin D became a popular supplement, and its use has increased markedly. The cost of establishing laboratory confirmation of vitamin D deficiency is high and as a result a significant proportion of vitamin D therapy is being prescribed empirically on clinical grounds exposing the population to the risk of vitamin D toxicity. An increased intake of vitamin D supplements by the general population and a growing number of prescriptions of therapeutic doses (including very high doses) without medical monitoring might result in a greater risk of exogenous hypervitaminosis D, with symptoms of hypercalcemia also known as vitamin D toxicity due to an overdosing and explains some of the problems of hypersensitivity to vitamin D.[4]

We report a rare pediatric case in whom empirical high-dose vitamin D supplementation led to acute toxic symptoms raising concerns requiring treatment.

CASE
A 6 yr old boy presented with history of loss of appetite since two months, irritability since two months, inability to walk since one month and increased frequency of micturition and bedwetting at night since fifteen days. Child was febrile for two days, two months back followed by loss of appetite, irritability and inability to do his routine daily activity, along with difficulty in walking which progressed gradually over 2 months till he could just take a few steps. He was diagnosed as autism spectrum disorder (ASD) at 3 years of age, and was on speech therapy for speech delay but not on any other medications. He was diagnosed to have vitamin D insufficiency 8 months back (VIT D:- 13.5 ng/ml) and was given cholecalciferol 60000 IU weekly for 6 weeks . However he had also received additional doses of VIT D from a general practitioner based on these reports which included injection cholecalciferol 200000 IU for 3 days. On examination the child was irritable, afebrile, heart rate-94/min, respiratory rate-24/min, blood pressure-100/60 mm of Hg. There was no pallor, icterus, edema, clubbing, lymphadenopathy or tenderness over spine or calf muscle. Child was irritable, cranial nerve examination was normal, tone and power was normal, b/l

plantars flexor, cerebellar signs could not be elicited, no signs of meningeal irritation.

Investigations: Complete blood count, renal function tests, liver function tests, thyroid function test and MRI brain were within normal limits. Serum and urine osmolarity done were 257mosm/kg (275-300) and 133mosm/kg (500-850) respectively which were below normal. S calcium- 13.5 mg/dl (8.5-11) was high, VitD3- 155.9 ng/dl is in toxicity level, PTH- 3.10 pg/ml was below normal, urine calcium / creatinine ratio of 0.23 was high suggestive of hypercalciuria.

Treatment: Supportive treatment was started and vitamin D and calcium supplements were discontinued .He was started on injection hydrocortisone 100 mg intravenously once daily for seven days followed by oral prednisolone 20 mg once daily for two weeks which was gradually tapered and stopped. After 5 days of treatment onset, irritability decreased and on day 7 child was walking comfortably and could climb stairs easily. His Vit D levels normalized over two months and he was able to do all his routine activities at follow up visits.

DISCUSSION

Vitamin D toxicity, also called hypervitaminosis D, is a rare but potentially serious condition that occurs when we have excessive amounts of vitamin D in our body. Vitamin D toxicity is usually caused by mega doses of vitamin D supplements — not by diet or sun exposure. That's because our body regulates the amount of vitamin D produced by sun exposure, and even fortified foods don't contain large amounts of vitamin D. Vitamin D toxicity causes hypercalcemia and multiple other adverse effects including potentially life-threatening ones.[5] Hypervitaminosis D with hypercalcemia may also be a manifestation of excessive production of $1,25(OH)_2D$ in granulomatous disorders, in lymphomas, and during idiopathic infantile hypercalcemia (endogenous VDT).[6]

Many forms of exogenous (iatrogenic) and endogenous VDT exist. Exogenous VDT is usually caused by the improper intake of extremely high doses of pharmacological preparations of vitamin D and is associated with hypercalcemia. Serum 25-hydroxyvitamin D [25(OH)D] concentrations higher than 150 ng/ml (375 nmol/l) are the hallmark of VDT due to vitamin D overdosing. Endogenous VDT may develop from excessive production of an active vitamin D metabolite – $1,25(OH)_2D$ in granulomatous disorders and in some lymphomas or from the reduced degradation of that metabolite in idiopathic infantile hypercalcemia. Endogenous VDT may also develop from an excessive production of 25(OH)D and $1,25(OH)_2D$ in congenital disorders, such as Williams–Beuren syndrome.

In endogenous VDT, hypercalcemia is related to increased $1,25(OH)_2D$ concentration; in contrast, in VDT due to an overdose of vitamin D (exogenous VDT), hypercalcemia is a consequence of high 25(OH)D concentration.[7]

Mechanism of vitamin D toxicity

It involves increased concentration of vitamin D metabolites reaching the vitamin D receptor (VDR) in the nucleus of target cells and causing exaggerated gene expressions. To explain this, the three hypothesis are as follows[8]:

1) Whenever there are increased levels of plasma 1,25[OH]D**,** it leads to increased intracellular concentration of the same. This hypothesis is not well supported as only one study who reported elevated 1,25[OH] D with Vit D toxicity, and many other studies revealed that vitamin D toxicity is associated with normal or marginally elevated 1,25[OH]D.[9]

2) Normal physiology is 1,25[OH] D has low affinity for the transport protein DBP and high affinity for VDR making it an important ligand with access to the transcriptional signal transduction machinery. In hypervitaminosis D various vitamin D metabolites increase, compromising the capacity of the DBP and allows other metabolites to enter the cell nucleus. Among these inactive metabolites 25[OH] D has the strongest affinity for the VDR, so at high concentrations it stimulates transcription.

3) Vitamin D intake raises the concentration of many vitamin D metabolites especially vitamin D itself and 25[OH] D. In hypervitaminosis D, vitamin D metabolites such as vitamin D3, 25[OH]D3, 24,25[OH]2D3, 25,26 [OH]2D3 and 25[OH]D3-26,23-lactone increase significantly. These concentrations exceed the DBP binding capacity and cause release of free 1-alpha 25[OH]2D3, which enters target cells.

Of those three hypotheses, abnormally high 25(OH)D and free $1,25(OH)_2D$ concentrations are the most credible, although even that concept remains unproven.[10],[11]

Clinical features

The clinical manifestation of VDT is due to hypercalcemia. Patient may present with following symptoms:-

1) CNS: Difficulty in concentration, confusion, apathy, lethargy, weakness, drowsiness, depression, psychosis, and in extreme cases stupor and coma.
2) CVS: Hypertension, shortened QT interval, ST segment elevation, and arrhythmias.
3) GI Symptoms: Recurrent vomiting, abdominal pain, polydipsia, anorexia, constipation, peptic ulcers, and pancreatitis.
4) RENAL: Hypercalciuria as the earliest sign, polyuria, polydipsia, dehydration, nephrocalcinosis, and renal failure.
5) OTHER: Band keratopathy, hearing loss, and painful periarticular calcinosis.[12],[13]

Diagnosis

Diagnosis of VDT require a detail history. Most of the cases of VDT is due to excessive dosages or too-frequent dosing intervals of vitamin D administered. General practitioners should be attentive to the symptoms of VDT in patients who have supplemented with therapeutic vitamin D doses or its metabolites.

Laboratory findings diagnostic of VDT are Hypercalcemia, Hyperphosphatemia, PTH decreased, Hypercalciuria, Raised 25(OH)D /1,25$(OH)_2$D concentration, ECG- arrhythmia, decreased QT interval

Vitamin D	Level (ng/dl)
Deficiency	<10
Insufficiency	10-30
Normal	30-100
Excess	100-150
Toxicity	>150

Exogenous VDT - 25(OH)D concentration>150 ng/ml (>375 nmol/l), and normal or increased values of 1,25$(OH)_2$D concentration, suppressed PTH.

Exogenous VDT due to acive metabolite[both 1,25$(OH)_2$D and 1α-OHD]- suppressed PTH (intact), elevated 1,25$(OH)_2$D concentration, and decreased or normal 25(OH)D concentration values.

Endogenous VDT- suppressed PTH (intact), decreased or normal 25(OH)D concentration, and elevated 1,25$(OH)_2$D.

In a hypercalcemic patient, hyperphosphatemia suggests VDT, whereas hypophosphatemia suggests primary hyperparathyroidism.[6],[14]

Treatment of acute VDT

Hypercalcemia due to a vitamin D overdose theoretically can last up to 18 months after the administration of vitamin D is discontinued. That is because of the slow release of the stored vitamin D from fat deposits. However, the half-lives of 25(OH)D and 1,25$(OH)_2$D in the body are much shorter, at 15 days and 15 h, respectively. Therefore, an overdose of 25(OH)D may persist for weeks, whereas that related to 1,25$(OH)_2$D lasts only a few days.[10],[15]

Treatment of VDT consists of [6],[12],[16]:

Discontinuation of vitamin D supplementation and the reduction of dietary calcium intake. The administration of isotonic sodium chloride solution to correct dehydration and restore kidney function is recommended. Glucocorticoids will decrease plasma calcium Glucocorticoids therapy changes the hepatic vitamin D metabolism to favor synthesizing inactive metabolites. Antiresorptive therapy with use of calcitonin, bisphosphonates Phenobarbital can be a useful treatment for VDT by decreasing 25(OH)D concentrations through induction of the hepatic microsomal enzyme.[17] Ketoconazole non-specifically decreases 1,25$(OH)_2$D production but long-term use is not recommended because it blocks many other important CYPs.[18] Aminoquinolines (chloroquine, hydrochloroquine) decrease 1,25$(OH)_2$D production.[19] In very severe cases hemodialysis can be done.

Recommended doses of Vitamin D

AGE	PREVENTION	TREATMENT OF INSUFFICIENCY	TREATMENT WITH LARGE DOSE (ORAL DOSE PREFERRED)
PREMATURE NEONATES	400 IU/DAY	1000 IU/DAY	NA
NEONATES	400 IU/DAY	2000 IU/DAY*	NA
1-12 MONTHS	400 IU/DAY	2000 IU/DAY*	60,000 IU/WEEK FOR 6 WEEKS(>3 MONTH AGE)
1-18 YEARS	600 IU/DAY	3000-6000 IU/DAY	60,000 IU/WEEK FOR 6 WEEKS

CONCLUSION

Although VDT resulting in hypercalcemia is rare, it can be life-threatening if not promptly identified. In the general population, the awareness of vitamin D–related health benefits is growing; however, the increased consumption of vitamin D–containing supplements may predispose the general public to an increased incidence of VDT. Therefore, without medical supervision, caution is advised for people who self-administer vitamin D at doses higher than recommended for age and body weight.

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