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Vitamin D Intoxication Presenting as Subacute Encephalopathy—A Case Report

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Abstract

Vitamin D intoxication is uncommon in children and is more commonly suspected in the setting of ingestion of high doses of vitamin D. Its manifestations can be non specific and varied ranging from mild like constipation and vomiting to life threatening like arrhythmias and encephalopathy. Here we present a 14 month female who presented with loss of milestones, floppiness, and poor interaction with mother. She was detected to have hypercalcemia and was subsequently diagnosed with vitamin D intoxication. She was successfully treated with hydration, furosemide, prednisolone and frequent monitoring of electrolytes, electrocardiography and volume status. Subsequently as her serum calcium levels normalized with therapy, she became alert, conscious and started achieving developmental milestones.

Keywords

Vitamin D, hypercalcemia, encephalopathy, hypotonia, prednisolone, diuretics, intoxication, pamidronate

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Vitamin D intoxication is rare in children due to a wide safety margin between therapeutic and toxic doses of the vitamin. Also chronic conditions like chronic kidney disease which predispose to vitamin D toxicity in elderly are uncommon in children. The spectrum of clinical features of vitamin D intoxication ranges from nausea and vomiting to some rare and serious conditions like hypotonia and encephalopathy. The diagnosis can be missed if there is no definite history of intake of large doses of vitamin D, although vitamin D toxicity can occur even at its supplemental doses due to difference in pharmacogenomics.

Case Summary

A 14 month previously healthy girl was brought to our institute with history of not able to sit, loss of neck control and inability to recognize and interact with mother for last 3 months, and vomiting for last 3 days. There was no history of fever, loose motions, convulsions, trauma, toxin ingestion or contact with tuberculosis. She was the only child of her parents born to non consanguineous couple. Antenatal, perinatal, neonatal, past and family histories were unremarkable. Her developmental milestones were normal till the age of 11 months.

On examination, she was lethargic, interacted poorly with mother and surroundings. She was hypotonic with frog-legged posture though spontaneous limb movements were present. Her vital parameters and hydration were normal. Her weight was 7.0 kg (-2.5 Z score), length 74 cm (-1 Z score), and head circumference 43 cm (-1.8 Z score). She had head lag on pull to sit, axial and appendicular hypotonia, power of all 4 limbs was at least grade III, deep tendon reflexes were non elicitable and bilateral plantar was down going. Rest of the systemic examination was normal. Work up for encephalopathy, neuroregression and hypotonia was done, suspecting inborn errors of metabolism.

Her complete blood count, renal and liver profiles, creatine kinase, thyroid function test (TFT), serum vitamin B12 levels and blood gas analysis were normal. Screening for amino acid disorders, organic acidemias and fatty acid oxidation defects on

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Table 1. Work Up For Hypocalcaemia in Child.

Laboratory test	Normal range	Lab value in baby	Interpretation of lab result in baby
Serum calcium (mg/dL)	9.00 to 11.00	15.70	High
Serum 25-hydroxy vitamin D (ng/mL)	More than 30.00 and less than 100.00	More than 150	Toxic range
Serum 1,25-dihydroxy vitamin D (pg/mL)	16.00 to 65.00	96.70	High
Serum intact parathormone (pg/mL)	18.50 to 88.00	Less than 0.23	Low
24 hours urinary calcium	Less than 4 mg/kg	80 mg in 24 hour	High

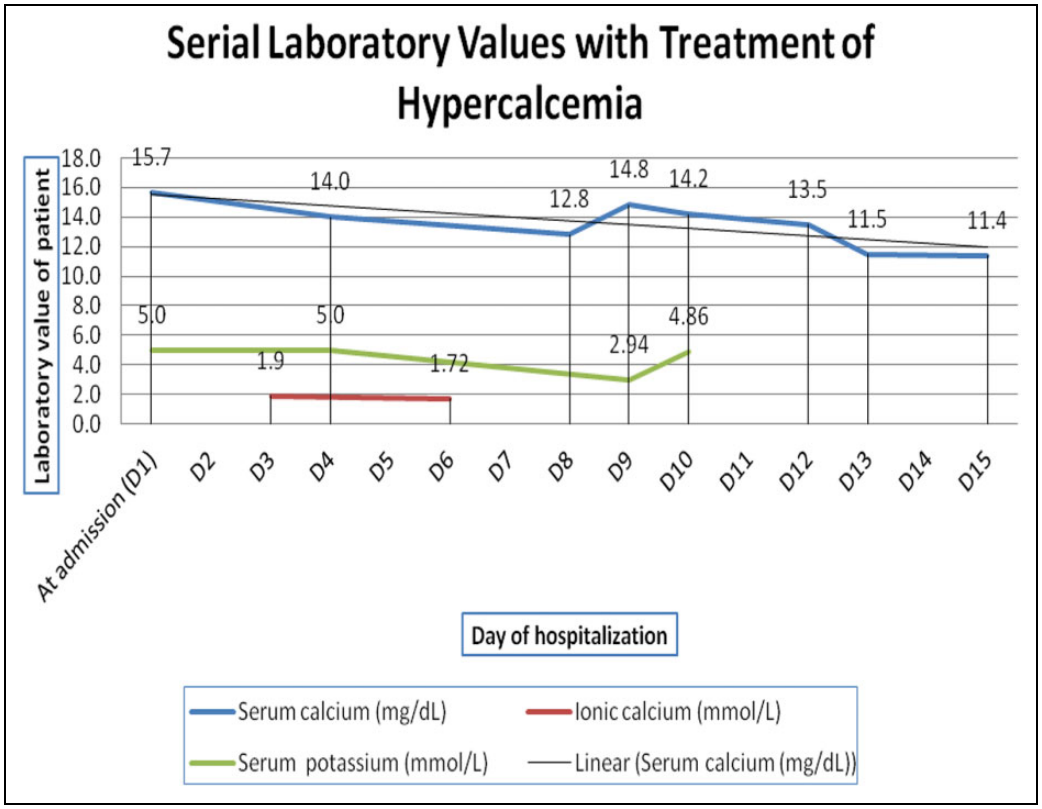

Figure 1. Serum electrolyte values during therapy.

dried blood sample by tandem mass spectrometry was normal. Electrocardiography (ECG) was normal with QTc 0.32 second. Ultrasound abdomen kidney ureter bladder, x ray abdomen (for nephrocalcinosis), echocardiography and magnetic resonance imaging (MRI) of brain was normal. Hearing assessment was normal. The only abnormality detected was high serum and ionic calcium levels of 15.7 mg/dL (normal 9.0 to 11.0 mg/dL) and 1.9 mmol/L (normal 1.22 to 1.37 mmol/L) respectively. Serum phosphorus and magnesium levels were normal.

Further work up for hypercalcemia revealed serum 25-OH vitamin D level in toxic range and low serum intact parathormone (PTH) level suggestive of exogenous vitamin D intoxication (Table 1).

On probing, parents revealed that baby had received 4 sachets of vitamin D orally, each of 60,000 IU (total 2.4 lakh IU) at an outside hospital and was not on any prolonged supplementation. Fluorescent in situ hybridization (FISH) targeted to the 7q11.23 region for Williams–Beuren syndrome (WBS) was done as dysmorphism in WBS is not easily appreciated in infancy and vitamin D intoxication in our case occurred at therapeutic doses and was negative; although WBS has global developmental delay rather than neuroregression and 80-90% cases have cardiovascular manifestations. Diagnosis of hypercalcemia secondary to vitamin D intoxication was made.

Child was treated with intravenous bolus of normal saline, followed by continued oral and/ or intravenous hydration at 1.5 to 2 times maintenance and intravenous furosemide 1.5 mg/kg/dose every 8 hours. Fluid volume status, electrolytes (including serum calcium) and ECG were monitored. During treatment baby developed hypokalemia which was managed as per protocol. With improvement of sensorium, baby was started on breast feeding and feeding via orogastric tube along with intravenous fluids. Serum calcium decreased but remained elevated after 8 days, so pamidronate was planned but could

not be given due to non-availability (Figure 1). Oral prednisolone 2 mg/kg/day was started. Serum calcium was near normal, and baby became alert, playful, started recognizing mother, regained social smile, started holding neck, and was sitting with support after 2 weeks of therapy, and was discharged with the plan to taper and stop prednisolone on follow up.

Discussion

Vitamin D is commonly prescribed due to the increased prevalence of vitamin D deficiency, awareness among health care workers about yet unproven role of vitamin D in various diseases, and the high cost of testing for serum vitamin D levels. Different preparations of vitamin D with various strengths are available over the counter. Despite of these facts, significant vitamin D toxicity is uncommon in children due to wide safety margin between its therapeutic and toxic doses. Elderly and those with renal involvement or primary hyperparathyroidism are predisposed to vitamin D toxicity [1].

The manifestations of vitamin D intoxication are mainly due to hypercalcemia; and include non specific features like fever, anorexia, nausea, vomiting, poor feeding, constipation, abdominal pain (colic), lethargy, irritability, weakness, confusion, dehydration, leg (bone) pain, failure to gain weight and weight loss; renal involvement in the form of polydipsia, polyuria, and nephrocalcinosis; and cardiovascular manifestations like hypertension, arrhythmias, shortening of QT interval and ST segment changes. Neurological manifestations like hypotonia, hyporeflexia, and encephalopathy as present in our case are less commonly reported.[2,3,4,5,6,7,8,9,10] Vitamin D intoxication may be incidentally detected due to hypercalcemia.[11,12]

Primary hyperparathyroidism presents with similar features, but has high PTH and low phosphorus levels. Granulomatous diseases like sarcoidosis and tuberculosis, prolonged immobilization and hyperthyroidism also cause hypercalcemia and were ruled out based on clinical examination and TFT. Familial hypocalciuric hypercalcemia presents with mild asymptomatic hypercalcemia and is associated with hypocalciuria.[13] WBS presents with dysmorphism, congenital heart disease (75%), developmental delay, hyperacusis, 'cocktail party' speech along with hypercalcemia. Hypercalcemia in WBS usually subsides during the first year of life, and PTH level is usually normal.[13]

Idiopathic infantile hypercalcemia (IIH) presents with hypercalcemia. It occurs due to homozygous or heterozygous loss-of-function mutation in CYP24AA1 gene.[14] CYP24A1 converts 1, 25-dihydroxy vitamin D to calcitroic acid and 25-hydroxy vitamin D to 24, 25-dihydroxy vitamin D. IIH remains a possibility in our case; it requires genetic testing for confirmation which was not done in our case due to high cost of testing and subsequent correction of hypercalcemia.

Vitamin D intoxication was diagnosed based on history, clinical features suggestive of hypercalcemia, elevated levels of calcium in serum and urine, reduced levels of serum intact PTH and serum 25-hydroxy vitamin D level more than 150 ng/mL.[3,15]

Management of hypervitaminosis D includes restriction of dietary calcium and vitamin D intake, appropriate volume repletion with isotonic sodium chloride solution, use of loop diuretics (furosemide), bisphosphonates (like pamidronate), steroids, and calcitonin.[3,4] Frequent monitoring of hydration status, serum electrolyte and ECG with replacement of ongoing losses of sodium, potassium, chloride and magnesium is important. Furosemide blocks reabsorption of sodium and calcium in thick ascending loop of Henle. Pamidronate is antiresorptive and causes more sustained decrease in serum calcium level. Adequate hydration must be ensured prior to use of pamidronate to prevent nephrotoxicity. Vitamin D stores in fat respond to glucocorticoids (hydrocortisone @100 mg/day or its equivalent). Prednisolone reduces intestinal calcium absorption, and is also effective in granulomatous diseases causing hypervitaminosis D. Long term use of steroids increases risk of skeletal fractures. Effect of calcitonin for management of hypercalcemia is short lasting. Other drugs like cinacalcet can be used in life threatening hypercalcemia, but it is not easily available.

Conclusion

Vitamin D intoxication is a reversible and easily treatable cause of hypotonia and encephalopathy in children, and should be suspected even in the absence of gastrointestinal symptoms and polyuria. This case also highlights that some individuals may have increased sensitivity to supplemental doses of vitamin D suggesting the role of genes in vitamin D and calcium metabolism, and that serum calcium and/ or vitamin D levels should be monitored at the slightest suspicion of its toxicity.

Author Contribution

NT, JT, and JS contributed to conception and design. All authors contributed to acquisition, analysis, and interpretation. All authors drafted manuscript, critically revised manuscript and gave final approval. All authors agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethical approval

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