J. Med. Toxicol. (2014) 10:190–193
DOI 10.1007/s13181-013-0365-0

TOXICOLOGY CASE FILES (FEATURE)

Vitamin D Toxicity in an Infant: Case Files of the University of California, San Francisco Medical Toxicology Fellowship

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Published online: 21 February 2014

Case Presentation

A previously healthy 2-month-old female with no significant past medical history and a normal birth history presented to her family doctor with 2–3 weeks of decreased activity and poor feeding. She was also noted to have diminished weight gain, decreased frequency of stools with only one stool over the previous 10 days prior to presentation, and a decrease in her urine output. There was no history of fever, upper respiratory symptoms, vomiting, or diarrhea, and there were no other sick contacts in the household. On physical examination, the patient was a well-developed and well-nourished female infant weighing 5 kg (33rd percentile). Vital signs were as follows: blood pressure 102/62 mmHg, pulse 140 beats per min, respiratory rate 24 breaths per min, and her temperature was 37.6 °C. The patient was described to have slightly diminished muscle tone throughout and decreased sucking reflex. No other abnormalities were noted.

What is the Differential Diagnosis for an Infant Presenting with These Symptoms? What Should the Initial Work-Up Entail?

The most concerning features of this infant's presentation include poor feeding associated with weight loss, a decrease in urine output, constipation and decreased activity with what appears to be a decrease in motor tone. While the constellation of symptoms leads to a broad differential diagnosis, the life-threatening causes that should be considered include acute infection or sepsis, metabolic and electrolyte abnormalities, inborn errors of metabolism, neurologic or cardiac disorders, child abuse, and toxic exposures.

Infection and sepsis in the infant may present with nonspecific symptoms such as poor feeding and decreased activity. The clinician should look for historical features and physical exam findings suggestive of infection and order appropriate diagnostic tests. Electrolyte abnormalities can also present with poor feeding and diminished activity. In particular, disorders of glucose, sodium, calcium, and magnesium may present with altered mental status or changes in motor tone as well as constipation. Endocrine abnormalities, such as hypothyroidism may also present in this fashion, as can a number of neurologic disorders and congenital cardiac abnormalities.

One must always consider inborn errors of metabolism (IEM) in any infant with diminished weight gain, changes in mental status, and poor feeding. Infants with metabolic disorders often present with nonspecific symptoms that may mimic other neurologic, infectious, and toxicologic emergencies. Vomiting, altered mental status, and difficulty feeding are perhaps the most prominent features of metabolic diseases. The physician should have a high suspicion for such disorders and careful history taking may reveal additional clues pointing to a specific disease [1].

Finally, there are a number of toxic exposures that could also be consistent with this presentation. Infant botulism should be considered and is characterized by hypotonia, constipation, tachycardia, poor feeding, and diminished motor tone [2]. Risk factors include age less than 1 year, breastfeeding, and ingestion of honey. Heavy metals such as arsenic, lead, and mercury can also cause lethargy and poor feeding. Intoxication by any number of drugs or medications could certainly present with decreased activity in the infant, and the physician should question family members about drugs and medications available in the home.

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Initial evaluation in this patient should focus on ruling out immediate life threats. Laboratory evaluation should include a complete blood count, urinalysis and urine culture, blood cultures, as well as consideration of a lumbar puncture. A chemistry panel including calcium, magnesium, and phosphorous should also be sent. Thyroid function studies should be sent as well as liver function tests and coagulation factors. If child abuse or neglect is of concern, the appropriate authorities should be contacted.

Case Continued

Further history from the mother revealed that the patient had been exclusively breast-feeding since birth. Her only medication was vitamin D, which she was taking for approximately 1 month prior to her presentation.

What is the American Academy of Pediatric Guideline Regarding Vitamin D Supplementation in Breast-Feeding Infants? Why are Infants Susceptible to Vitamin D Deficiency and What are the Consequences of Vitamin D Deficiency?

In 2008, the American Academy of Pediatrics issued guidelines that recommended doubling the amount of vitamin D supplementation for all infants from 200 to 400 IU/day [3]. This guideline was established in response to increasing concerns regarding infant susceptibility to vitamin D deficiency. Vitamin D is essential for bone growth and development in children and adolescents. The clinical manifestations of vitamin D deficiency include rickets, characterized by defective bone formation, and osteomalacia. It is thought that children are increasingly prone to vitamin D deficiency due to lower dietary intake of vitamin D and inadequate sun exposure [3].

Case Continued

The patient's laboratory data were significant for a serum calcium of 19.1 mg/dL (8.8–11.3 mg/dL). The rest of the serum chemistry panel were as follows: sodium 141 mEq/L, potassium 3.1 mEq/L, chloride 108 mEq/L, bicarbonate 15 mEq/L, BUN 15 mg/dL, creatinine 0.6 mg/dL, glucose 119 mg/dL, magnesium 1.6 mg/dL, and phosphorus 4.8 mg/dL.

What is the Mechanism of Calcium Homeostasis in the Body? What is the Differential Diagnosis for Hypercalcemia in this Infant and What Additional Testing is Necessary to Narrow the Differential Diagnosis?

The skeleton contains 98 % of total body calcium. The remaining 2 % circulates in the blood. Plasma calcium levels are maintained by the interplay between tubular reabsorption in the kidneys, absorption from the small intestine, and bone remodeling [4]. Maintenance of normal calcium levels is under tight regulation by parathyroid hormone (PTH) and vitamin D. PTH is secreted by the parathyroid glands and increases serum calcium by direct action on osteoclasts in bone, and by activation of vitamin D in the kidney. Vitamin D is synthesized from cholesterol in the skin in response to sunlight. It is converted in the liver to 25-hydroxyvitamin D, and further metabolized in the kidney to the active form 1,25-dihyroxyvitamin D.

It is helpful to consider the causes of hypercalcemia as either PTH-dependent or PTH-independent (see Table 1). PTH-dependent causes include primary hyperparathyroidism, malignancies associated with elevated PTH-related protein, and genetic syndromes. PTH-independent causes also include malignancies and genetic conditions in addition to drug-related etiologies. High calcium intake rarely results in hypercalcemia in the adult and usually occurs in patient with concomitant chronic kidney disease and a significant decrease in calcium excretion. In contrast, in the small infant, hypercalcemia can occur with ingestion of calcium-enriched formulas [4].

Further investigation should focus on measuring intact serum PTH in order to distinguish primary hyperparathyroidism from PTH-independent causes of hypercalcemia. Elevated serum PTH levels support the diagnosis of primary hyperparathyroidism. PTH concentrations below 20 pg/mL usually are not consistent with primary hyperparathyroidism, and vitamin D levels and PTH-related protein levels should be checked in such cases to help determine an alternative cause of hypercalcemia.

Describe the Various Drug-Induced Causes of Hypercalcemia. How Do They Result in High Calcium Levels?

Vitamin D intoxication is a well-described cause of hypercalcemia [5]. Toxic effects of hypercalcemia from hypervitaminosis D are usually evident when intake of vitamin D exceeds

Table 1 Selected causes of hypercalcemia

Parathyroid hormone dependent	Parathyroid hormone independent
Hyperparathyroidism	Iatrogenic
Congenital parathyroid hyperplasia	Phosphate depletion
Maternal hypoparathyroidism	Premature infants on human milk or standard formula
Inactivating mutations in calcium sensing receptor gene	Parenteral nutrition
Familial hypocalciuric hypercalcemia	Inborn metabolic disorders
	Hypervitaminosis A
Neonatal severe hyperparathyroidism	Hypervitaminosis D
	Drugs (Thiazides, Lithium)

25,000 IU/day and the serum 25-hydroxyvitamin D level is at least 200 ng/mL [6]. Hypervitaminosis D has been attributed to over-fortification of milk [7, 8], infant formula [9], over-the-counter vitamin D supplements [10, 11], contaminated foods [12], and dosing errors [13]. A recent Food and Drug Administration MedWatch Safety Alert warns parents of the risk of infant overdoses related to liquid vitamin D [14].

Hypervitaminosis A can also cause hypercalcemia [15]. Animal studies and in vitro studies have demonstrated that vitamin A increases osteoblastic activity and enhances osteolysis in rats [16]. Receptors for retinoic acid are located on both osteoclasts and osteoblasts [17], suggesting a direct effect of vitamin A on bone.

Lithium-induced hyperparathyroidism can also result in hypercalcemia [18]. It is estimated that approximately 10–15 % of patients treated with lithium become hypercalcemic with findings suggestive of hyperparathyroidism [19]. It appears that lithium-associated parathyroid hyperplasia is independent of the dosage and duration of treatment.

Thiazide diuretics are reported to cause hypercalcemia, and at least one case with a calcium level as high as 19.8 mg/dL has been reported [20]. The mechanism is likely related to enhanced reabsorption of calcium from the distal convoluted tubule of the kidney. Most cases are associated with underlying hyperparathyroidism or another concurrent condition predisposing to hypercalcemia.

Case Continued

Additional history obtained from the mother revealed that her vitamin D prescription called for 1 mL (400 IU vitamin D per mL) to be taken daily. The vitamin D supplement purchased online was a concentrated form containing 400 IU per drop. A previously published report of a similar vitamin D overdose [4] demonstrated that 1 mL was equivalent to approximately 30 drops; the patient was therefore receiving roughly 30 times the intended daily dose of vitamin D (12,000 IU per day) for approximately 1 month. According to the Institute of Medicine, the level above which there is risk for adverse events in the neonate (0–6 months of age) is 1,000 IU per day [6]. The patient's 25-hydroxyvitamin D level was measured at 750 ng/mL (normal 25–80 ng/mL), and her PTH level was measured at less than 3 pg/mL (consistent with expected resultant PTH suppression).

What Treatments are Available for Patients with Hypercalcemia? How Does Each of These Treatments Work?

All vitamin D supplementation should be discontinued immediately. In addition, the majority of symptomatic children with hypercalcemia are dehydrated at presentation from reduced fluid intake and the diuretic effect of calcium. Rigorous hydration with 0.9 % saline alone is often an effective treatment. A loop diuretic such as furosemide is rarely necessary and can increase the risk of excessive diuresis and dehydration, as well as the development nephrocalcinosis [4].

Bisphosphonates reduce plasma calcium levels by inhibiting osteoclastic bone resorption. Examples of these agents include alendronate, ibandronate, and pamidronate. These agents can lower serum and urinary calcium levels in patients with hypercalcemia due to a variety of causes and the effects can last for weeks. Patients must be monitored carefully however, as these agents may result in hypocalcemia, hypophosphatemia, and hypomagnesemia and comprehensive clinical trials on the safety and efficacy of these agents in children are lacking [4].

Calcitonin is safe and relatively nontoxic. It interferes with osteoclast function resulting in decreased bone resorption. The efficacy is limited to the first 48 h after the first dose is given due to downregulation of calcitonin receptors. Because of this limited duration of effect, calcitonin is most beneficial in symptomatic patients with calcium levels greater than 14 mg/dL when combined with hydration and a bisphosphonate. Calcitonin and hydration provide a rapid decrease in serum calcium, while bisphosphonates provide a longer and sustained effect. The usual recommended starting dose of calcitonin is 2–4 IU/kg intramuscularly or subcutaneously every 12 h. The dose can be increased up to 6 to 8 IU/kg every 6 h. A common side effect of calcitonin is mild nausea and rarely acute hypersensitivity reactions.

Finally, hemodialysis is effective in reducing serum calcium concentrations and can be considered as a potential adjunct to the above therapies in conditions of symptomatic hypercalcemia necessitating rapid correction.

Case Continued

The patient was admitted to the hospital and treated with normal saline. She was given calcitonin 20 IU SC q 12 h, pamidronate 3.75 mg IV q 24 h, and methylprednisolone 5 mg IV q 12 h. Her calcium levels declined over the course of 1 week to 9.6 mg/dL (see Table 2). Her clinical condition

Table 2 Trend in serum calcium levels over time

Hospital day	Ca (mg/dL)
1	19.1
2	14.3
3	13.0
4	12.1
5	11.9
6	10.0
7	9.6

gradually improved and she was discharged on hospital day 7 in good condition.

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