Global Advanced Research Journal of Medicine and Medical Science (ISSN: 2315-5159) Vol. 4(3) pp. 098-101, March, 2015
Available online http://garj.org/garjmms/index.htm

Case Report

Just from innocent omega 3 supplementation to nephrocalsinosis

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Accepted 12 March, 2015

Hypervitaminosis D caused by the use of multivitamin preparations, including vitamin D, or of vitamin D added to milk preparations is another example. It leads to hypercalcemia and secondary hypercalciuria. We present case of vitamin D toxicity due to manufacturing errors of prescribed omega multivitamin supplements resulted in detrimental nephrocalsinosis and treatment of hypercalsemia with pamindronate.

Keywords: nephrocalsinosis, omega 3, hypervitaminosis D

INTRODUCTION

Hypercalcemia is defined as serum calcium >12 mg/dl (>3 mmol/l). Severe hypercalcemia is defined as serum calcium >15 mg/dl (3.75 mmol/l). We can classify hypercalcemia reasons under three main etiologies. First is hyperparathyroidism can be primary hyperparathyroidism (adenoma, multiple endocrine neoplasias, calcium-sensing receptor mutation-loss of function, secondary or tertiary hyperparathyroidism (e.g., chronic kidney disease). Second is excess vitamin D because of hypervitaminosis D, sarcoidosis, granulomatous diseases (Wegener's, Crohn's disease), cat scratch disease, tuberculosis. Third are the factors releasing calcium from bone such as thyrotoxicosis or immobilization.

Hypercalciuria can result from genetic or acquired aetiologies, detected as a risk factor for urolithiasis in a child (Pont, 1989). The gastrointestinal tract, bone, and kidneys play major roles in calcium metabolism under the influence of diet, phosphorus, fluid and electrolyte homeostasis, PTH, calcitonin, and vitamin D metabolites.

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Although idiopathic hypercalciuria remains the commonest form of hypercalciuria, a systematic search for secondary causes of hypercalciuria should be made when clinically or biochemically suspected.

Hypercalciuria is well described in patients with a history of hypercalcemia or vitamin D excess (Ronnefarth and Misselwitz, 2000). Hypercalciuria is common to many of these conditions (Sayer et al., 2004; Ronnefarth and Misselwitz, 2000). Hypervitaminosis D caused by the use of multivitamin preparations, including vitamin D, or of vitamin D added to milk preparations is another example. It leads to hypercalcemia and secondary hypercalciuria. Nephrocalcinosis is the term used for deposits of calcium salts in the tubules, the tubular epithelium, or the interstitial tissue of the kidney. It is usually diagnosed at the macroscopic level by ultrasonography.

Nephrocalcinosis is classified according to the anatomic area involved. Medullary nephrocalcinosis is differentiated from either cortical (e.g., in acute cortical necrosis, chronic glomerulonephritis, and chronic graft rejection) or diffuse nephrocalcinosis. Nephrocalcinosis is commonly related to tubulopathies such as Dent disease, Bartter syndrome, and Lowe syndrome, and it is also observed in patients with primary hyperoxaluria and distal

Table 1. Laboratory values of serum creatinine Ca, P, PTH, 25 OH D vitamin levels and urine Ca/creatinine values of case during follow up.

Treatment Time	Serum kreatinin	Ca	P	PTH	ALP	Mg	25 OH Vitamin D ng/ml	Urine Ca/Creatinine
1st day	0,6	17,8	4,7	2,65	89	1,8	361	0,6
7 th day (pamindronate started)	0,5	16,8	4,6		111	1,16	>70	0,8
11th day at fourth dosage of pamindronate	0,4	12,7	3		163	1,18	>70	0,9
14 th day	0,6	11,7	2,1		177	1,1	>70	0,59
30 day	0,3	9,3	2,3		256	1,44	>70	0,06
3th month	0,3	9,94	5,63	30,7	249	1,7	49,8	0,05
6th month	0,5	10,2	5,6	28,6	269		49,5	0,02
1st year	0,3	10,1	6,1	27,7	241		30,5	0,05
18th month	0,3	10,2	5,6	20,1	303	1,8	51,4	0,07
2th year	0,5	9,8	4,9	52,4	258	1,84	28,05	0,05
3th year	0,5	10,6	5	24,4	198	1,86	31,9	0,06

renal tubular acidosis (Sayer et al., 2004).

We present case of vitamin D toxicity due to manufacturing errors of prescribed omega multivitamin supplements resulted in detrimental nephrocalsinosis and treatment of hypercalsemia with pamindronate.

THE CASE

A 2-month-old boy was admitted with weight loss, vomiting, and poor breast feeding. Before coming to our nephrology department, local physician was diagnosed him as urinary tract infection. Enterobacterium species 10^6 colony/ml was grown in his urine culture. Renal ultrasonography showed an image consistent with bilateral nephrocalcinosis. He referred for further diagnosis of nephrocalcinosis. His medical history was unremarkable. The patient's body weight was 3.1 kg (- SDS), height 58 cm (- SDS), and head circumference cm (- SDS). On physical examination he was hypotonicity and had moderate dehydration, other systemic signs were normal.

Laboratory parameters were as following: serum ionized C:2,33 mmol/L,Albumin 3,9 mg/dl Ca: 17,4 mg/dL (N=8.4-10.2), P: 4,77 mg/dL (N=2.7-4.5), ALP:89, creatinine: 0.8 mg/dL (N=0.5-1.3), PTH: 2,65 pg/mL (N=15-65), 25(OH) vitamin D: 361 ng/mL (N=25-80), and urinary Ca/creatinine ratio: 0,6 (N<0.21), TPR 90 %. The patient was started treatment with 150 mL/kg/day intravenous (IV) hydration and 2 mg/kg/day furosemide. Serum Ca was 16.5 mg/dL at 24 hours, and prednisolone 1 mg/kg/day was also added to the treatment regimen. On day 5, persistent hypercalcemia was ongoing, due to pamindonate nonexistence, calcitonin was given at the dosages of 4 unite/kg for two days. After we reach the drug at 7 th day, pamidronate was started 0,5 mg/kg intravenously over 6 hours. After second dose of pamindronate serum Ca level was decreased from 18,5 to 16.5 mg/dL. Pamindronate was given total of four daily doses and at 5 th day of pamindronate serum Ca level was 11,7 mg/dl He had been given an omega preparation with multivitamin once daily (containing 200 IU/day vitamin D) for 3 days, prescribed by her physician for poor appetite. The preparation was prescribed by her physician as a dietary supplement.

In order to reveal etiology, detailed laboratory and clinical investigations were done. Thyroid function tests and thyroid and parathyroid ultrasonography were normal. Echocardiography showed patent foramen ovale and his findings were inconsistent with Williams's syndrome. His mother blood was analysed for CA, P, ALP, PTH and vitamin D and the results were normal.

During her hypercalcemia treatment she had high fever and respiratory difficulty chest radiography revealed developed bronchopneumonia. For suspicion of hemophagocytic lymphohistiocytosis and malignancy, bone marrow aspiration was done and it was found normal. Sepsis was managed successfully by intensive inotropic support and antibiotic treatment. Laboratory values of serum creatinine Ca, P, PTH, 25 OH D vitamin levels and urine Ca/creatinine values of our case are shown in table 1.

DISCUSSION

Hypercalcemia is one of the very important and dangerous electrolyte imbalances. The first step in the diagnostic evaluation of hypercalcemia is to ensure that the alteration in serum calcium levels is not due to abnormal albumin concentrations. Because about 50% of total calcium is ionized, and the rest is protein bound mainly to albumin (Ozkan et al., 2012; Handbook of Fluid, Electrolyte, and Acid-Base Imbalances). Our case serum

albumin was normal and measured ionized serum calcium level was very high (2,33 mmol/L). When we investigated etiological factors, excessive use of calcium including supplements was suspected reason. Other causes of hypercalcemia were excluded. His kidney function tests were normal and there were no any laboratory signs of cellular destructions like malignancy (Ozkan et al., 2012).

Hyperparathyroidism increases the production of PTH then PTH promotes the release of calcium from the bone (Ozkan et al., 2012). Once true hypercalcemia is established, most important laboratory tests in the diagnostic evaluation are PTH and 1, 25(OH) vitamin D level. Serum creatinine should be measured to assess renal function; because hypercalcemia may impair renal function, and renal clearance of PTH may be altered depending on the fragments detected by the assay. If the PTH level is increased (or inappropriately normal) in the setting of an elevated calcium and low phosphorus, the diagnosis is almost always primary hyperparathyroidism (Handbook of Fluid, Electrolyte, and Acid-Base Imbalances). A suppressed PTH level in the face of hypercalcemia is consistent with non-parathyroid-mediated hypercalcemia (Handbook of Fluid, Electrolyte, and Acid-Base Imbalances) as in our case. His serum parathormone was suppressed with an elevated level of 25(OH) vitamin D (361 ng/mL).

Furthermore we should keep in mind that serum 1, 25(OH) D vitamin levels are also increased in granulomatous disorders (Handbook of Fluid, Electrolyte, and Acid-Base Imbalances), our case had no any clinical signs of granulomatous diseases.

Symptoms of vitamin D intoxication including loss of appetite, vomiting, constipation, growth retardation, polyuria, dehydration, and fever are secondary to hypercalcemia. Our case presented with loss of appetite and vomiting dehydration and poor feeding, indicating typical vitamin D intoxication. Hypercalciuria and nephrocalcinosis are characteristic laboratory findings of vitamin D intoxication observed due to hypercalcemia (Araki et al., 2011). Medullary nephrocalsinosis was seen on renal ultrasonographic images.

Vitamin D intoxication due to manufacturing errors of dairy products during the enrichment process of vitamin D to reduce nutritional rickets has been reported before (Ozkan et al., 2012). Araki et al reported two adult cases of vitamin D intoxication with dietary supplements caused by significant manufacturing and labelling errors that lead to 1000 fold higher levels in vitamin D content (Handbook of Fluid, Electrolyte, and Acid-Base Imbalances).

A detailed history was provided important clue regarding the etiology of hypercalcemia. There were a suspicious three dosage of omega with multivitamin supplement intake .Nevertheless preparations ingested by the patient was not sent to analyse using the High Performance Liquid Chromatography method. We could not establish that the ingredient vitamin D present in the product was 25 (OH) vitamin D but there were no any other convicted substance intake.

We urgently monitored his vital signs, and ECG strips for noting any change. First exogenous vitamin D intake is discontinued. Increased hydration is very crucial to increase calcium dilution and prevention of renal calculi formation in the treatment. We increased our patient fluid intake and gave iv hydration to dilute the serum and urine levels of calcium and to prevent the formation of renal calculi. His urinary output and urine pH were closely monitored. Loop diuretics were administered to enhance calcium excretion but not Thiazide diuretics. Thiazides inhibit calcium excretion and are not indicated in hypercalcemia (Baroncelli and Bertelloni, 2014). Glucocorticoids were given also. As in our case severe persistent hypercalcemia, calcitonin and bisphosphonates (pamidronate) may be used (Araki et al., 2011). Hemodialysis is also effective way to reduce the serum calcium level rapidly especially in refractory cases to medical treatment (Handbook of Fluid, Electrolyte, and Acid-Base Imbalances). Our case became normocalcemic after bisphosphonate usage. Bisphosphonates block bone resorption over 24-48 hours by shortening the life span of osteoclasts. they decrease serum calcium in 2-4 days with a nadir at 4-7 days. These medication have been studied more in adults than in children; however, many studies have established safety and efficacy in children, particularly with etidronate and pamidronate (Baroncelli and Bertelloni, 2014). We safely used pamindronate and it effectively decreased our patients serum calcium in 5 days.

CONCLUSION

Vitamin D supplements (400 IU/day) are regularly prescribed to infants in all over the world. In addition multivitamin preparations containing vitamin D are given to infants as nutritional supplements. We thought that the preparations ingested by the patients as a supplement had high levels of vitamin D which might have led to intoxication. Physicians must be careful and have evidence based proposals while prescribing nutritional supplemental products in order to prevent irreversible damages. Biphosphanates can be used safely in treatment of hypercalcemia treatment of children.

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