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CASE REPORT

Hypercalcemia, hypercalciuria and nephrocalcinocis associated with high vitamin D intake in an infant

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We report an eight month – old female infant who presented with hypercalcemia, failure to thrive, polyuria and dehydration following excess vitamin D supplementation: the first eight months of life. At birth, she weighed 3000 gr and at admission to the hospital her weight was 6700 gr. She presented serum calcium concentration 3.6 mmol/l, calciuria 14 mg/kg and the renal ultrasound revealed nephrocalcinosis.

The intact PTH was low (< 3 pg/ml). Although 25(OH) vitamin D_3 plasma level was not measured. After rehydration and after evaluation of the prevailing pathogenic mechanism, prednisone was given for treatment of hypercalcemia. The beneficial response, with no recurrence of hypercalcemia / hypercalciuria after discontinuation of prednisone and introduction regular milk formula, provides strong evidence that hypercalcemia, hypercalciuria and nephrocalcinosis were due to vitamin D intoxication.

To diagnose vitamin D intoxication, one must consider it in the differential diagnosis and obtain a history of vitamin D intake in infants with hypercalcemia / hypercalciuria and failure to thrive of obscure origin.
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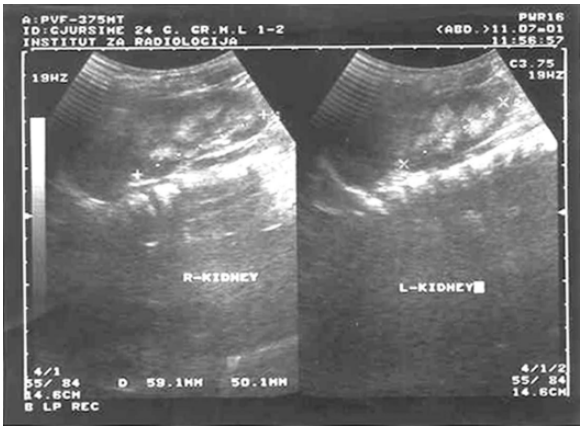
Hypercalcemia associated with hypercalciuria and nephrocalcinosis is rare in infancy. The causes me be diverse[1]. The most common cause is iatrogenic, then idiopathic infantile hypercalcemia (IIH) in its mild or severe form (Williams's syndrome). Vitamin D intoxication is a rare cause for clinically manifested hypercalcemia and is associated with prolonged morbidity. It may be due to endogenous synthesis of 1,25 dihydroxyvitamin D (subcutaneous fat necrosis and granulomatous disease) or to excessive exogenous vitamin D intake. Hypercalcemia can be parathyroid related (primary or secondary hyperparathyroidism), or tumor related as a result of increased levels of parathyroid hormone related protein (PTHrP). Hypercalcemia occurs in Jansen's Syndrome, hypophosphatasia, hypophosphatemia, vitamin A intoxication, blue – diaper syndrome or in association with some medications, such as hydrochlorothiazide. Since sequels of hypercalcemia could be serious, particularly renal consequences which include nephrocalcinosis, nephrolithiasis and renal failure, these children must be investigated promptly and treated adequately.

Case Report

An eight month old female was admitted at our department because of ultrasonografic finding of medullar nephrocalcinosis (Fig. 1). Her past medical history was unremarkable except for polyuria, polydipsia and failure to thrive noticed within the last 2-3 months. She was feeding poorly, receiving standard cow's milk based formula. At birth she weighed 3000 gr and her length was 50 cm. At admission to the hospital her weight was 6700 gr (3rd percentile). She had been taking vitamin D at prophylactic doses 1200 U/d, for the first three months of life (5 gouts of Plivit D_3). Thereafter, she was switched to Vigantol (5 gouts/d, equivalent to 3300 U/d), for five months. On admission, except for malnutrition, dehydration and irritability, her physical examination revealed no abnormality. Her temperature was 38^0 C, the heart rate 130 beats/min and the blood pressure 90/60 mmHg. There were no dismorphic facial features. Routine laboratory tests revealed normal hemogram, normal values of sodium, potassium, chloride and magnesium. In several occasions hypercalcemia (calcium 3.6 mmol/l) was confirmed with an ionized Ca of 1.8 mmol/l. Phosphorus was 1.6 mmol/l and alkaline phosphatase 170 U. Blood glucose was 5.3 mmol/l, uric acid was 355 U/l, vitamin A 140 U/l. Hepatic tests (AST, ALT, and bilirubin) were normal. Blood gasses obtained to distinguish renal tubular acidosis were within normal limits (pH 7.4, HCO3 22.8 mmol/l). Thyroid hormone levels were in normal range. PTH was < 3 pg/ml (normal range 11-62 pg/ml). Urine analysis performed on several occasions showed normal urinary sediment. Urinary cultures were negative. Specific gravity of spot urine was 1003, pH 5 and 24 hour urine volume 1000-1400 ml. There was hyperuricosuria.

In several occasions there was marked hypercalciuria with urinary calcium creatinine ratio (mmol/mmol) ranging from 2.5 – 3.5 and calciuria of 14 mg/kg. The parents

Figure 1. *Renal ultrasound: medullar nephrocalcinosis*



of the child were also investigated and both had normal serum calcium levels and a normal urinary calcium creatinine ratio.

Complete Fanconi syndrome was excluded due to the lack of glucosuria and hyperaminoaciduria. Clinically and on the chest X ray there was no evidence of granulomatous disease (such as sarcoidosis). Radiological examination of the wrist did not show any evidence of rickets excluding hypophosphatasia. Echocardiography did not reveal subvalvular stenosis and there was no typical "elfin like" face, features excluding William's syndrome.

The vitamin D was promptly discontinued and the diet was changed to a non – fortified diet containing no supplemental vitamin D, using solids and excluding milk and milk products. The treatment consisted of intravenous fluids (with 150 – 200 ml/kg/24h) for stimulating calcium diuresis and 1.5 mg/kg, prednisone divided in three doses over one month period, for decreasing hypercalcemia. One month after discharge she was in good condition with normal state of hydration, diuresis of 500 ml/24h, and weight gain of 500 gr. Laboratory tests revealed serum calcium of 2.6 mmol/l and calciuria of 10 mg/kg, the last normalized subsequently after 3 months. The standard milk formula and "ad libitum" calcium intake was introduced thereafter.

At the age of 2 years and 8 months the child shows normal physical and mental development. Her growth improved: height is now over the 75 percentile and weight on the 90 percentile. Calcemia is 2.2 mmol/l and calciuria 2 mg/kg. The medullar nephrocalcinosis although slightly improved is still present on ultrasound.

Discussion

The infant with persistent mild or profound hypercalcemia requires urgent diagnostic evaluation[1-3]. Measurement of an intact PTH level, at the time of hypercalcemia is pivotal. If it is high, the infant must be thoroughly investigated for hyperparathyroidism, and may require urgent surgical intervention. If the PTH level is low as in our patient, additional calcitrophic hormones must be assayed. Identifying the abnormal calcitrophic hormone might allow the diagnosis of a specific syndrome, elucidation of the mechanism for the hypercalcemia and definition of the optimal treatment. Unfortunately these investigations are not always available in all centers, as in present patient. Therefore we had to use an indirect approach in the differential diagnosis of his hypercalcemia.

Familial hypocalciuric hypercalcemia is an autosomal dominant disease, usually characterized by asymptomatic hypercalcemia primarily due to increased proximal tubular resorption of calcium leading to hypocalciuria and normal or inappropriately increased serum concentrations of PTH. It arises as a result of molecular defect in the calcium – sensing receptor; loss of function or activating mutation has been described[4]. In our patient, hypercalciuria (instead of hypocalciuria) and normal calcium status in both parents excluded this possibility indirectly.

We considered also the possibility for idiopathic infantile hypercalcemia (IIH). It is a rare cause of hypercalcemia in the first year of life and initially was considered part of a spectrum encompassing vitamin D intoxication, William's syndrome and idiopathic hypercalcemia[1,5]. Identification of the gene for William's syndrome now allows a clear separation of IIH from Williams's syndrome. Generally, hypercalcemia in IIH resolves by 12 months of age and the prognosis is good.

Vitamin D intoxication still has to be considered as a possible cause of hypercalcemia with hypercalciuria[6,7]. Excessive endogenous synthesis of 1,25 dihydroxyvitamin D can occur in conditions such as subcutaneous fat necrosis and granulomatous disease. Since our patients had no characteristic clinical symptoms or signs such diseases were excluded indirectly. In addition, as there were no symptoms or signs suggesting William's syndrome, Jansen's syndrome, hypophosphatasia, malignancy or vitamin A intoxication, these conditions were excluded.

Vitamin D therapy was responsible for 9% of 152 children and adolescents with nephrocalcinosis in 22 German centers of pediatric nephrology[8]. Our patient has been receiving very high "prophylactic" dose of vitamin D. The mother has been giving incorrectly 5 gouts / d using two different forms of vitamin D supplements. She did not take in consideration that the supplement contained different amount of vitamin D, giving to the child 3300 U daily for 5 months.

The established prophylaxis for vitamin D-deficient rickets today is 2000 IU vitamin D3 given daily during the first year of life, and the tolerable upper intake level is indicated as 50 micrograms per day (2000 IU/d)[9].

Biological half – life of vitamin D is long and hypercalcemia and hypercalciuria could persist for months. Severe hypercalcemia may be life threatening and requires prompt management[1,10].

After rehydration, which is an essential first step in

the management strategy, and after evaluation of the prevailing pathogenetic mechanism, the acute treatment will be aimed at the increasing urinary Ca excretion and inhibiting bone resorption. Our patient showed beneficial answer to prednisone, with no recurrence of hypercalcemia / hypercalciuria after discontinuation of prednison and introduction of a regular milk formula. Such clinical course provides strong evidence that hypercalcemia, hypercalciuria and nephrocalcinosis were due to vitamin D intoxication.

In conclusion we described an infant with hypercalcemia, hypocalciuria and nephrocalcinosis associated with high oral intake of vitamin D. We depicted the clinical course and differential diagnostic considerations. To diagnose vitamin D intoxication one must consider it in the differential diagnosis and obtain a history of vitamin D intake in infants with hypercalcemia / hypercalciuria and failure to thrive of obscure origin. In severe cases of vitamin D intoxication, glucocorticosteroids are useful for short – term management. Renal nephrocalcinosis may persist despite symptomatic and biochemical improvement.

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