CASE REPORT

IATROGENIC VITAMIN D INTOXICIATION IN INFANCY: THREE CASES

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ABSTRACT

The potential hazards of excessive administration of vitamin D are well known. The increased intestinal absorption of calcium due to vitamin D over dosage leads to hypercalcemia and hypercalciuria that may give rise to the development of nephrocalcinosis, urolithiasis, and soft tissue calcification. Clinical features of three cases of iatrogenic vitamin D intoxication with different radiological findings were presented. The dose of vitamin D should be carefully determined in order to avoid vitamin D intoxication, and its complications. In addition, public health measures should be undertaken to prevent drug consumption without prescription that may be dangerous especially for children.

Key words: Vitamin D, Intoxication, Nephrocalcinosis, Children

SÜT ÇOCUKLARINDA İYATROJENİK D VİTAMİNİ İNTOKSİKASYONU:ÜÇ OLGU

ÖZET

D vitaminin aşırı kullanılmasının potansiyel yan etkileri iyi bilinmektedir. D-vitaminin aşırı kullanılımı barsaktan kalsiyum emilimini artırıp hiperkalsemi ve hiperkalsiüriye; bu ise nefrokalsinozis, ürolitiyazis ve yumuşak dokuda kalsifikasyonlara yol açabilir. Farklı radyolojik bulguları olan üç iyatrojenik D-vitamini intoksikasyonu olgusunun klinik özellikleri sunulmuştur. D vitamini intoksikasyonundan ve komplikasyonlarından kaçınılması için D-vitamini dozu dikkatli hesaplanmalıdır. Ayrıca, çocuklar için zararlı olabilecek ilaçların reçetesiz satılması engellenmelidir.

Anahtar kelimeler: Vitamin D, Zehirlenme, Nefrokalsinozis, Çocuk

INTRODUCTION

The potential hazards of excessive administration of vitamin D are well known. There are many reports related with usage of high doses of this vitamin; in the treatment of resistant rickets, hypoparathyroidism, renal osteodystrophy and over dosage in infants [1–5]. The increased intestinal absorption of calcium due to vitamin D over dosage leads to hypercalcaemia and hypercalciuria that may give rise to the development of nephrocalcinosis, urolithiasis, and soft tissue calcification [2-4].

Three cases of iatrogenic vitamin D intoxication with different radiological findings are presented here.

CASE REPORT

Case 1

A two-month-old girl was admitted to our clinic with complaints of failure to thrive, loss of weight and irritability. When she was 30 days old, one ampoule (300,000 IU) of vitamin D per week had been tailored orally to induce growth by her parents without any advice of a medical doctor. Cumulative dose of ingested vitamin D was 1,200,000 IU per month. Physical examination revealed the weight below 3%, pallor and irritability. The rest of the physical examination was normal. The urinalysis revealed isostenuric urine with a density of 1015, a trace of protein, and many leucocytes and calcium phosphate crystals in the urine sediment.

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The serum levels of urea, creatinine, sodium, potassium, uric acid were normal, but serum calcium, phosphorus and alkaline phosphatase levels were 18 mg/dl, 5.6 mg/dl and 400 IU/L, respectively. Her urinary calcium/creatinine ratio was 3.1 (N: < 0.21). The parathormone level was 5.1 pg/ml (N: 12-72), and 25-hydroxy vitamin D level was >160 ng/ml (N: 10-40). Abdominal ultrasound revealed bilateral medullary nephrocalcinosis (Fig. 1).

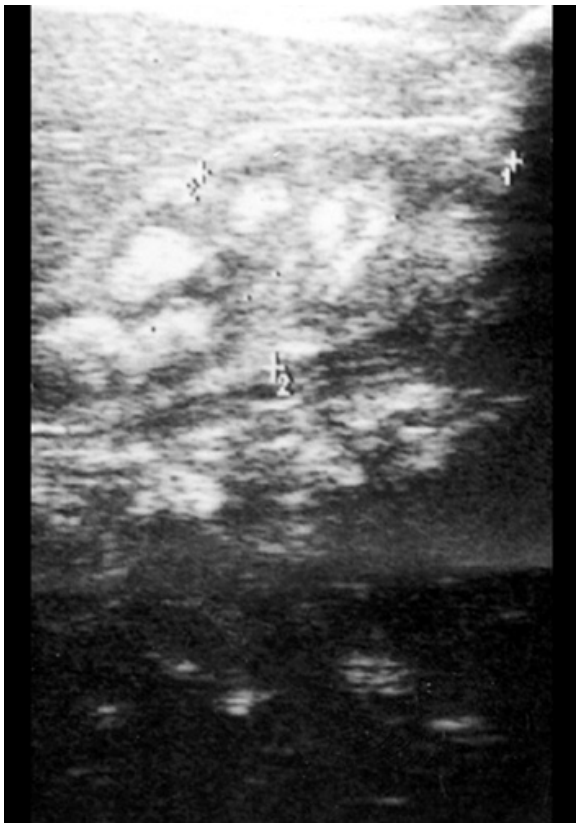

Figure.1 Bilateral medullary nephrocalcinosis

A probable diagnosis of vitamin D intoxication was made on the basis of the medical history, clinical and laboratory findings.

She was admitted to intensive care unit and monitorized. Vitamin D administration was ceased, and the treatment consisting of hydration with parenteral fluids (3000 ml/m^2/day, 1/3 normal saline) and corticosteroid (2 mg/kg/day) was started. The level of serum calcium decreased and returned to normal limits in six days. The corticosteroid dose was reduced slowly and ceased in 15 days. Neither hypercalsemia nor hypercalciuria was detected after the treatment, and urinary calcium/creatinine ratio was decreased to 0.12. The infant was discharged with the recommendation of a high fluid intake. During her one-year out-patient follow-up, bilateral nephrocalcinosis has continued for three months, and then improved.

Case 2

An 8-month-old boy was admitted to our clinic with complaints of diarrhea and decreased appetite. From his medical history, it was learned that two ampoules (300,000 IU) of vitamin D had been administered orally without any advice of a medical doctor in order to induce growth by his parents. On physical examination, pectus excavatum and mild dehydration findings were determined. His height and weight were between the 90th and the 97th percentile. The rest of physical examination was unremarkable. Complete blood count and urinalysis and serum levels of urea, creatinine, sodium, potassium, uric acid were normal, but serum level of calcium was 11.7 mg/dl, phosphorus was 7.0 mg/dl and alkaline phosphatase was 684 IU/L. The urinary calcium/creatinine ratio was 0.58 (N: < 0.21). The parathormone level was 29.4 pg/ml (N: 12-72) and 25-hydroxy vitamin D level was 90 ng/ml (N: 10-40). Abdominal ultrasound showed bilateral minimal calcification on renal parenchyma. Vitamin D intoxication was diagnosed in the light of the medical history, clinical and laboratory findings.

Emergency treatment, consisting of IV hydration (3000 ml/m^2/day, 1/3 normal saline) and corticosteroid was initiated. The serum calcium level was decreased and returned to normal limits value in four days. The corticosteroid dose was reduced slowly and stopped in 15 days. After the discontinuation of the corticosteroid administration hypercalsemia and as well as hypercalciuria was recovered and urinary calcium/creatinine ratio were decreased to normal limits. The infant was discharged with the recommendation of a high fluid intake. His out-patient follow-up was uneventful for two years and the renal parenchyma returned

to normal morphology in the third month of the follow-up.

Case 3

A 20-month-old girl with epilepsy was admitted to our clinic with complaints of seizures, vomiting and fever. One ampoule (300,000 IU) of vitamin D per day had been given orally by her parents for five days (a total dose of 1,500,000 IU) for inducing the ability of walking without any advice from a medical doctor. On physical examination, fever, drowsiness and motor-mental-retardation were noticed. On laboratory investigations, the serum levels of urea, creatinine, sodium, potassium, uric acid were normal, but serum calcium level was 15.5 mg/dl, phosphorus level was 4.1 mg/dl and alkaline phosphatase level was 132 IU/L. The urinary calcium/creatinine ratio was 4.2 (N: < 0.21). The parathormone level was 10.1 pg/ml (N: 12-72), and 25-hydroxy vitamin D level was >160 ng/ml (N: 10-40). Abdominal ultrasound was normal. The patient was diagnosed with vitamin D intoxication on the basis of the medical history, clinical and laboratory findings.

We speculate that seizures occuring in this case were not only related to over dosage of vitamin D, because she had mental retardation and had had seizures before the administration of over-dose vitamin D. Hypercalcaemia had not been detected before the vitamin D over dosage.

Administration of vitamin D was ceased immediately and the treatment consisting of hydration with parenteral fluids (3000 ml/m^2/day, 1/3 normal saline) and corticosteroid (2 mg/kg/day) for 15 days was started. On 7^{th} day of the treatment, her serum calcium level and urinary calcium/creatinine ratio returned to the normal limits. The patient was discharged with the recommendation of high fluid intake orally.

DISCUSSION

The physiological effect of vitamin D in pharmacological doses is to increase gastrointestinal calcium and phosphate absorption and to increase bone resorption, presumedly the high 25-hydroxy vitamin D levels stimulate both the intestinal and bone 1, 25 dihydroxy vitamin D receptors [1, 2, 4]. Vitamin D that is administered over therapeutic doses leads to intoxication in infancy [1, 2]. The typical manifestations of vitamin D toxicity are attributed mainly to the resultant hypercalcemia. These include anorexia, failure-to-thrive, vomiting, constipation, irritability, convulsions, polyuria, polydipsia, dehydration and fever [1–6]. The initial complaints of our patients were different and presented such as failure-to-thrive, loss of weight, irritability (Case 1); diarrhea and decreased appetite (Case 2) and fever, seizures, and vomiting (Case 3).

The characteristic laboratory findings of vitamin D intoxication are high serum calcium level, normal or high serum phosphate level, elevated alkaline phosphatase, low parathormone and high vitamin D levels. Hypercalcemia resulting from vitamin D intoxication is always associated with hypercalciuria. The diagnosis of vitamin D intoxication is made by determining the serum 25-hydroxy-vitamin D level [2, 4]. The serum levels of calcium, parathormone and 25-hydroxy vitamin D and urinary calcium /creatinine ratio were all consistent with vitamin D intoxication in our patients.

Hypercalcemia leads to nephrocalcinosis by overloading the renal resorptive mechanism. A high calcium load causes cellular damage followed by calcium salt deposition in tubular cells, in basement membrane epithelium, and within the loop of henle [2, 3]. The classical distribution of nephrocalcinosis is along the corticomedullary junction. Generally nephrocalsinosis does not demonstrate any pathologic findings on plain abdominal X-ray or computed tomography. Ultrasonographic examination reveals medullary nephrocalcinosis [2,6,7]. In our patients, different ultrasonographic findings were determined. The patients did not reveal any history for renal diseases upto the administration to our hospital. The different findings in ultrasound examination were not correlated with dosages of vitamin D, so it can be speculated that

clinical outcome can be associated with personal peculiarity and fluid intake. In addition; hypercalcemia can rarely cause keratopathy in the cornea and ectopic calcifications in the lung, heart, large vessels, skin [4].

The mainstay of therapy for vitamin D intoxication depends on hydration with intravenous saline followed by loop diuretics, glucocorticoids, diet consisting of low calcium and phosphate, and of course discontinuation of vitamin D and calcium supplementation. Glucocorticoids decrease intestinal absorption of calcium and decrease bone resorption and should be taken less than one week to normalize the serum calcium in patients with hypervitaminosis D [1, 2, 4, 8].

Recently; another effective treatment modality for the hypercalcemia related to vitamin D over dosage seems to be bisphosphonates, especially oral alendronate administration. It has been published that short-term oral alendronate sodium treatment had been effective to normalize hypercalcemia/hypercalcuria, had decreased the duration of hospitalization, and had been safe during 15-months observation in infant with vitamin D intoxication [9]. Bereket and Erdoğan [9] concluded that brisk response to alendronate sodium treatment might have provided further evidence that hypercalcemia in vitamin D intoxication is related with increased bone turnover.

Hatun and Çizmecioğlu [10] reported that; initiating bisphosphonates in early stages in patients with vitamin D intoxication had been appropriate in order to prevent or minimize nephrocalcinosis. It has been advised that; treatment with alendronate sodium should be continued until normocalcemia has been established [10]. Up to today many authors have reported that the use of oral alendronate had been an alternative to parenteral bisphosphonates in patients with vitamin D hypervitaminosis and seems to be a more practical and effective treatment choice [10, 11]. Bisphosphonates, especially oral alendronate plays an important role in the treatment of hypercalcemia associated with vitamin D intoxication by inhibiting octeoclast activity. It has been thought that alendronate treatment for all cases is not needed, because conventional treatment modalities such as intravenous hydration, loop diuretics, glucocorticoids are considered satisfactory.

Other conventional modalities for the treatment of hypercalcemia associated with hypervitaminosis D include mithromycin and calcitonin that inhibit osteoclast function; sodium cellulose phosphate which increases fecal calcium excretion; phenobarbital, phenytoin and gluthemide which induce hepatic microsomal enzymes and therefore accelerate vitamin D metabolism [4-8].

The treatment in our cases consisted of discontinuation of vitamin D administration, hydration with intravenous 1/3 normal saline, followed by glucorticoid administration until the serum calcium levels and urinary calcium / creatinine ratio became to the normal limits.

As a result, we would like to vigorously emphasize that the dose of vitamin D should be carefully determined in order to avoid vitamin D intoxication. In addition, public health measures should be undertaken to prevent drug consumption without prescription that may be dangerous especially for children.

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