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NEPHROCALCINOSIS DUE TO VITAMIN D INTOXICATION*

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The toxic effects of excessive administration of vitamin D (Vit D) have been known for a long time. The characteristic features of Vit D toxicity were described in animals by Kreitmair and Moll[1] in 1928, and in the same year Hess and Lewis[2] reported clinical hypervitaminosis D in man. Since then, many reports on Vit D toxicity have been published concerning pharmacologic doses of this vitamin in the treatment of hypothyroidism, resistant rickets, renal osteodystrophy and overdosage in infants[2-9].

Hypercalcemia resulting from Vit D overdosage is a life-threatening condition which develops because of an increase in intestinal calcium absorption. Acute or chronic hypercalcemia may lead to the development of nephrocalcinosis by overloading the renal resorptive mechanism, and also to urolithiasis and soft tissue calcification[5,6,9-12].

The purpose of this study is to describe two cases of nephrocalcinosis caused by Vit D intoxication, review the clinical, biochemical, and radiologic findings of Vit D intoxication, and briefly discuss its treatment.

Case Report

Case 1

A three-month-old male infant was admitted to the Hacettepe University Children's Hospital with complaints of vomiting and lethargy of 10 days' duration. He had been treated twice previously for a diagnosed urinary tract infection. He had polyuria for the last 15 days. On further questioning, it was learned that Vit D had been administered to the patient in a dose of 45,000 IU/day for the last 45

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days. Physical examination revealed a subfebrile infant with a pulse rate of 144/min. The fontanel was slightly depressed (2 × 2 cm). Turgor and tonus were decreased. The infant, who seemed to be lethargic, had depressed eyeballs and dry oral mucosa. The other findings of the physical examination were normal.

Laboratory data revealed a hemoglobin level of 11.2 g/dl and a white blood cell count of 9,000/mm^3. The BUN was 10 mg/dl, HCO^-_3 27.96 mEq/lt, serum Na^+ 153 mEq/lt, K^+ 4.2 mEq/lt, calcium 19.5 mg/dl, phosphorus 2.6 mg/dl and alkaline phosphatase 3.6 BU. Urinalysis revealed hyposthenuric urine with a specific gravity of 1002, a trace amount of protein, no glucosuria and many leukocytes and calcium phosphate crystals in the urinary sediment. The urinary calcium/creatinine ratio was 1.3. Two consecutive urine cultures were found to be sterile. The urinary and serum amino acids were normal. Abdominal ultrasonography demonstrated bilateral medullary nephrocalcinosis (Fig. 1). No pathologic findings were seen on the IVP. A probable diagnosis of Vit D intoxication was made on the basis of the patient's clinical and laboratory findings and medical history. Treatment consisted of infusing 1/3 serum physiologic solution (3500 cc/m^2) and furosemide (4 mg/kg/day). A corticosteroid was also given (2 mg/kg/day) for 15 days. The patient was followed up closely for signs of dehydration and electrolyte imbalance. When the serium calcium level returned to normal, the infant was discharged with the recommendation of a high fluid intake.

Case 2

A four-month-old male infant was admitted to the Hacettepe University Children's Hospital with complaints of vomiting, lethargy and failure-to-thrive. He had had projectile vomiting for the last 10 days. It was noted that Vit D had been administered to the patient in a dose of 60,000 IU/day for the last month.

Physical examination revealed an afebrile infant with a pulse rate of 136/min and a respiratory rate of 34/min. The patient's general appearance and other findings of the physical examination were normal. Laboratory data revealed a hemoglobin level of 10.5 g/dl and a white blood cell count of 8,000/mm^3. The BUN was 14 mg/dl, serum calcium 17.6 mg/dl, phosphorus 3.8 mg/dl, alkaline phosphatase 10 BU, serum Na^+ 134 mEq/lt, K^+ 3.9 mEq/lt, and Cl^- 104 mEq/lt. Urinary examination revealed a specific gravity of 1002, trace amount of protein with 4-5 white blood cells per high magnification field in the urine sediment. Urinary culture yielded *E. coli* 10,000 microorganisms/ml but there were no microorganisms on a repeat culture. The urinary calcium/creatinine ratio was 0.7. There were no pathologic findings seen on the plain abdominal, and hand and wrist roentgenograms, or on the intravenous pyelogram. Abdominal ultrasonography revealed densely echogenic pyramids (Fig. 2). A probable diagnosis of Vit D intoxication was made on the basis of the patient's clinical, laboratory and radiological findings.

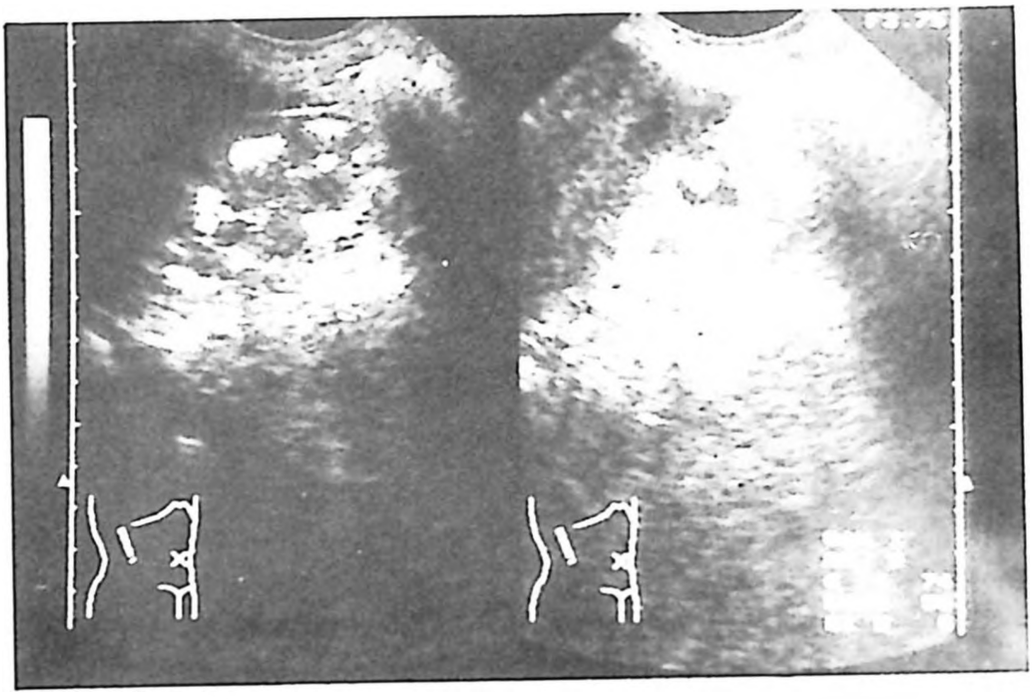

Fig. 1: Striking medullar nephrocalcinosis demonstrated during abdominal ultrasonographic examination.

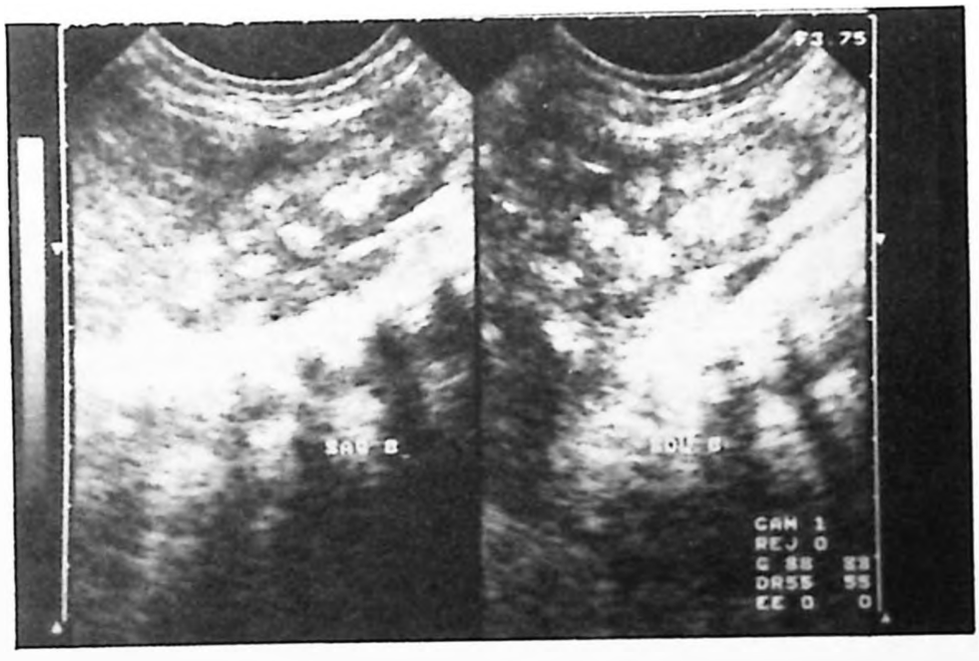

Fig. 2: The cortex of the kidney is normal. Medullary pyramids are seen as hyperechoic without acoustic shadowing.

The therapy initated was the same as for Case 1. When the serum calcium level returned to normal, the patient was discharged.

During the follow-up, the serum calcium and phosphate levels were normal, but the control ultrasonographic examination still showed medullary nephrocalcinosis six months after discharge.

Discussion

It is well known that pharmacologic doses of Vit D and a dose of over 400 IU/day in infancy results in Vit D intoxication[2-9,12]. Samir and Yazigi[5] reported fifteen cases of Vit D intoxication after the administration of 1.25 to 2 million IU of Vit D for a period of from one to four months. 30,000-60,000 IU/day of Vit D were administered to our patients for a period of from one to three months.

The typical manifestations of Vit D toxicity are attributed mainly to the resultant hypercalcemia. These include anorexia, failure-to-thrive, vomiting, constipation, irritability, convulsions, polyuria, polydipsia, dehydration and fever[5,9,12].

A potential renovascular effect of acute hypercalcemia leads to vasoconstriction in the renal arterioles which in turn decreases the glomerular filtration rate and the activation of the renin angiotensin system causes hypertension[9,12,13]. Our patients were admitted to the hospital with complaints of fever, vomiting, lethargy, dehydration and failure-to-thrive. Hypertension was not recorded in our cases. These findings were similar to the other cases reported.

The characteristic laboratory findings of Vit D intoxication are a high serum calcium level, normal or high serum phosphate level, and elevated alkaline phosphatase levels. Hypercalcemia resulting from Vit D intoxication is always associated with hypercalciuria[5,6,9,12]. Hypercalciuria is defined as urinary calcium excretion above 4 mg/kg/day or a urinary Ca/Cr ratio of the morning sample of over 0.21[9]. Hyposthenuric urine is frequently seen in cases of Vit D intoxication due to prepication of urinary calcium in the renal tubular cells. Hyposthenuric urine was also noted in our cases.

Hypercalcemia leads to nephrocalcinosis by overloading the renal resorptive mechanism[11]. A high calcium load causes cellular damage followed by calcium salt deposition in tubular cells, basement membrane epithelium, and within the loop of Henle. The classic distribution of nephrocalcinosis is along the corticomedullary junction[9-12]. Ultrasonography is superior to other radiological examinations with the exception of CT scanning[10,14] in demonstrating this type of abnormality. In our cases there were no pathologic findings on plain abdominal x-ray or intravenous pyelography. Ultrasonographic examination demonstrated medullary nephrocalcinosis.

Hypercalcemia also causes nephrolithiasis which is due to intratubular calcification and, less frequently, ectopic calcifications in the lung, heart, large vessels and skin, and band keratopathy in the cornea[9,12]. However, we did not observe such calcification in our patients.

Normal 1.25 $(OH)_2$ Vit D plasma concentrations have been reported in patients with hypervitaminosis D[15]. The diagnosis of Vit D intoxication is made by determining the serum 25-hydroxy Vit D (25-OH D) level[4,7,8]. In our cases, the 25-(OH) D level could not be measured.

The therapeutic approach to Vit D intoxication is symptomatic by putting the patient on a low calcium and Vit D-free diet, preventing exposure to the sun, and lowering the serum calcium levels[5,6,9,12,16]. Corticosteriods are used to prevent calcium reabsorption from the intestine and to increase calciuria[9,16]. Bromocriptine which is known to inhibit prolactin release, has been demonstrated to reduce serum calcium levels resulting from hypervitaminosis D in rats[17].

Furosemide-induced hypercalciuria is dependent on the natriuretic effect of this diuretic. After rehydration treatment, furosemide should be given until the serum calcium levels return to normal. Calcitonin is beneficial in cases of hypercalcemia accompanied by an acute decrease in neurologic, cardiovascular and renal functions[16].

Treatment in our cases consisted of rehydration with 1/3 serum physiologic infusion (3500 cc/m^2) followed by furosemide (4 mg/kg/day p.o) and prednisolone (2 mg/kg/day p.o) administration until the serum calcium levels returned to normal. During the follow-up period, the serum calcium levels were found to be normal, but the nephrocalcinosis persisted six months after discharge.

In the light of our experience with our two patients, the prescribed dose of Vit D should be carefully determined in order to prevent Vit D intoxication, and its complications. In addition, drug consumption without prescription, which is a big problem in developing countries, should be avoided.

Summary

Two cases of vitamin D intoxication are presented. The patients, one aged three months, and the other aged four months, were given Vit D in doses ranging from 30,000 IU/day to 60,000 IU/day for over a period of from one to three months.

Laboratory data showed serum calcium levels of 17.6-19.5 mg/dl and phosphorus levels of 2.6-3.2 mg/dl. Renal ultrasonographic examination demonstrated medullary nephrocalcinosis in both patients.

In this study the clinical, biochemical and ultrasonographic findings and the therapy of Vit D intoxication are reviewed, and preventive measures are suggested.

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